VOLUME 54 NUMBER 1

# ARCHIVES OF

# NEUROLOGY AND PSYCHIATRY



JULY 1945

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO 10, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second Class Matter Jan. 7, 1919, at the Postoffice at Chicago, Under the Act of Congress of March 3, 1879

# CONTENTS OF PREVIOUS NUMBER

## JUNE 1945. NUMBER 6

# ARCHIVES OF

# NEUROLOGY AND PSYCHIATRY



VOLUME 54
1945

PUBLISHERS
AMERICAN MEDICAL ASSOCIATION
CHICAGO, ILL.

# CONTENTS OF VOLUME 54

## JULY 1945. NUMBER 1



## AUGUST 1945. NUMBER 2

AUGUST—*Continued*



SEPTEMBER 1945. NUMBER 3



OCTOBER 1945. NUMBER 4

OCTOBER—*Continued*



NOVEMBER-DECEMBER 1945. NUMBER 5

NOVEMBER-DECEMBER—*Continued*

Archives of Neurology and Psychiatry

VOLUME 54 JULY 1945 NUMBER 1



# EXTINCTION AND PRECIPITATION OF CUTANEOUS SENSATIONS

LIEUTENANT COMMANDER M. B. BENDER, MC(S), U.S.N.R.

It is generally assumed that the cutaneous modalities of one side of the body are represented in the opposite side of the brain. Conventionally, a lesion in the right parietal lobe causes a decrease in sensation on the left side of the body. However, there is also clinical and physiologic evidence indicating that certain parts of the body are bilaterally represented in the parietal cortex. Foerster [1] electrically stimulated the sensory cortical area in man, with the result that the patient complained of bilateral paresthesias. Dusser de Barenne [2] reported that painting a small part of the arm area in one parietal cortex with strychnine produced hypersensitivity in both arms in the monkey. Other than these investigations, there are relatively few studies demonstrating a functional relationship between the sensations of the two halves of the body, such as stimulation of the skin on one side influencing the cutaneous sensation on the opposite side of the body.

In a previous communication, a competitive relationship between the visual sensation in the right and that in the left homonymous fields was described.[3] One side was found to influence the other, and it was hypothesized that the healthy side dominated and inhibited the diseased side. In a patient who survived a gunshot wound of the left occipitoparietal cortex, it was found that when visual stimuli were simultaneously exposed on the two sides of a fixation point he perceived the image on the left side, while the image on the right appeared dull and obscure or became totally extinct. When the object in the normal field was removed, he clearly perceived the object remaining in the affected field of vision. Furthermore, it was noted that the more visual stimulation there was on his left side, the less he saw in the right field of vision. The phenomena of visual obscuration and extinction described illustrate a functional relationship between the two occipital lobes. Now, if such phenomena are demonstrable in the visual perceptive spheres, it is reasonable to assume that they should also be found on testing the cutaneous modalities under the same conditions. As a matter of fact, Oppenheim,[4] in 1900, casually mentioned the phenomenon in describing a method for sensory examinations, stating:

> In certain brain diseases which cause unilateral disturbance of sensibility the following procedure is advantageous. Stimulate simultaneously two symmetrical points. The patient will always detect it only on the sound side, whereas in single tests he may detect every stimulation of the affected side. The manner of examination, we would call the method of double stimulation.

From these observations it is apparent, then, that the phenomena of obscuration and extinction should be generally applicable to most forms of sensation. With this in mind, groups of patients with cutaneous sensory disturbances due to lesions at different levels of the nervous system were studied. The object of the investigation was to determine the nature and degree of sensory dulling or extinction with the method of double stimulation and to learn with what types of lesions these functional disturbances could be obtained. While the study was in progress, another group of patients was found in which a stimulus on the normal side precipitated or aggravated a burning pain on the opposite, or affected, side. The pain in the affected side was limited to the palm and fingers or to the sole and toes in a limb which was causalgic as a result of a nerve injury.

## MATERIAL AND METHOD

Patients with gunshot wounds of the brain, spinal cord, nerve roots or peripheral nerves were studied. For obvious reasons, only subjects with a clear mind, good orientation and reasonable intelligence were considered. Whenever it seemed indicated, special tests of memory, retention, reasoning ability and imagination were given to determine the presence or absence and, if present, the degree, of intellectual impairment.[5] Many of the patients were studied over prolonged periods, and the changes in restitution of function were recorded. Special attention was given to: (1) the sensory response to "double stimulation" with mixed and uniform types of stimuli; (2) the temporal factors

1. Foerster, O., cited by Dusser de Barenne.[2]

2. Dusser de Barenne, J. G.: Central Levels of Sensory Integration, A. Research Nerv. & Ment. Dis., Proc. **15**:274, 1935.

3. Bender, M. B., and Furlow, L. T.: Phenomenon of Visual Extinction in Homonymous Fields of Vision and Psychological Principles Involved, Arch. Neurol. & Psychiat. **53**:29 (Jan.) 1945.

4. Oppenheim, H.: Diseases of the Nervous System, translated by E. E. Mayer, Philadelphia, J. B. Lippincott & Co., 1900, p. 59.

5. These tests were performed by Lieut. Comdr. A. L. Benton, H-(V)S, U.S.N.R.

in sensation, such as (*a*) sensory adaptation time,[6] (*b*) duration of after-sensation and (*c*) rate of fluctuation of sensation, and (3) spatial factors in cutaneous sensibility, such as (*a*) graphesthesia, or the ability to perceive figures drawn on the skin, (*b*) perception of direction of lines drawn on the skin and (*c*) ability to localize points touched or otherwise stimulated on the skin.

In eliciting the response to double, or simultaneous, cutaneous sensory stimulation, care was taken to insure that the applied stimuli were of equal strength. In a few instances the two points of a compass were simultaneously applied to each of the two corresponding parts of the body, the points being equally distant from the midline. For testing pain modality in most cases, graduated algesiometers, from 2.5 to 25 Gm., with a no. 10 needle point were used. For tactile sensation, small wisps of absorbent cotton were applied to the skin. Thermal sensibility was tested with small cold or warm metal objects. For vibration sense, a tuning fork of 128 vibrations per second was used. Other sensations tested were discrimination of weight, stereognosis and two point discrimination. Graphesthesia was elicited by writing with a pencil on the skin the number *4*, the letter *E*, a triangle, a circle and a square. With the double stimulation method, an image was drawn on one side and a few nondescript lines were simultaneously drawn on the other side of the body. The time relations for sensory adaptation, after-sensation and fluctuation in sensation were measured in seconds with a stopwatch.

## REPORT OF CASES

### CEREBRAL LESIONS

CASE 1.—N. G. K., a Marine veteran aged 29, was admitted to the hospital in May 1944 because of dizzy spells and convulsive seizures. In 1936, he was accidentally shot, and the bullet lodged in the right side of his brain. There was immediate left hemiplegia, which subsequently receded. One year after injury, there appeared spells of falling and unconsciousness; despite this, he was able to work as a laborer until a few weeks prior to the present admission to the hospital, when the attacks became more frequent and severe.

Physical examination gave essentially normal results. There was a bony defect in the right parietal bone. Neurologic examination disclosed left hemiparesis with moderate spasticity involving mostly the distal portions of the arm and leg, concomitant signs referable to the pyramidal tract and noticeable atrophy of the affected extremities. In addition, strong clenching of the right fist caused involuntary flexion at the left hand and elbow, flexor movement at the knee and foot and sometimes spasm of the face. The functions of the cranial nerves were essentially normal except for diminished taste sensation on the left side. The visual acuity, visual fields and tachistoscopic perception were normal.

*Sensation.*—The patient complained that occasionally he did not know the whereabouts of his left hand, that the left side of his body felt numb and that he was unable to detect objects with his left hand.

The sensory defects were limited to the left side of the body. Pain and temperature sensations were reduced on that side, especially in the distal portions of the extremities. The response to painful stimulation varied. Frequently, the patient perceived a distinct point, but this sensation did not last long. During continual application of a 15 Gm. stimulus on the left forearm, the pain changed to a dull pressure sensation within two seconds, and the latter disappeared entirely within seven seconds. In the corresponding area on the right side, the same stimulus produced sense of pain for fifteen seconds and sense of pressure for over sixty seconds. In other words, the sensory adaptation time was greatly reduced on the affected side, especially in the distal portions of the extremities. As compared with the normal side, the adaptation time for pain and touch modalities was much shortened on the affected side, the sensations lasting only one second or disappearing immediately. Superficial tactile sense was diminshed over the same distribution as pain and temperature modalities. Fine tactile sense was absent over the left extremities, especially in the distal portions, and it was variably diminished over the trunk and the face. Vibration sense was preserved, whereas the senses of position and initiation of movement were lost completely in these limbs. The patient was unable to detect gross movements of the fingers or slow movement at the wrist and made errors in appreciation of the posture of the forearm. Stereognosis was lost in the affected hand, foot and side of the mouth. He was unable to detect the presence of a cigaret or to recognize objects with the left side of the lips as well as he did with the right side. Point localization was slightly impaired. He was unable to determine the direction or the type of lines drawn on the skin over the distal parts of the extremities. All he perceived was a movement associated with the deep pressure sense. He had pronounced agraphesthesia in these zones. Over the trunk he was sometimes able to detect a circle, a triangle, the letter *E* and the number *4* when drawn on the skin. In other areas on his left side he did not even attempt to guess at the applied stimulus.

As already noted for pain, all sensations showed a notably reduced adaptation time. Duration of after-sensation was also diminished. In several instances, the pain sense revealed fluctuation phenomena, in spots there being two or three variations between the pain and the pressure sensation.

*Sensory Extinction Phenomenon.*—Simultaneous application of painful stimuli to corresponding foci on the two sides of the body produced (*a*) reduction in adaptation time, (*b*) a sharp rise in the sensory threshold, so that he felt no pain at all or just a dull sense of pressure, or (*c*) total extinction of the perception on the left side of the body. When the stimuli were applied separately, he was able to appreciate a sharp point on each side of the trunk. With "double stimulation" he often was unaware that anything was touching him on the left side, unless the stimulus on the right side was removed within the sensory adaptation time for the left side. When the stimuli were unequal—for instance, 25 Gm. on the left side and 10 Gm. on the right—dulling of sensation still occurred on the left side. When the stimulus was stronger on the right side, the phenomenon was even more apparent, sensation on the left side becoming totally extinct.

The phenomenon could also be produced with simultaneous applications of mixed stimuli. The extinction phenomenon for the tactile sense on the left side could always be elicited by a simultaneous painful stimulus on the right side. The same was true when conditions were reversed; i. e., with a tactile stimulus on the

6. Psychologically, all sensations show the phenomenon of negative adaptation. Under continual and unchanging application of a given stimulus, the characteristic sensation evoked disappears after a given interval. This interval is termed "the sensory adaptation time" in this paper and should not be confused with the word "adaptation" as used in the physiologic sense by Adrian and others.

right side, the pain sense was inhibited or obliterated on the left side. The vibration sense was not inhibited on the left side with double stimulation; painful, tactile or other forms of stimuli applied to the right side did not obliterate the vibratory stimulus applied simultaneously to the left side. However, vibratory stimuli on the right side did inhibit painful and tactile stimuli on the left side.[7]

Tactile perception of movement, such as rubbing or scratching, along the skin of the left hand was preserved. But when both the right and the left hand were rubbed simultaneously, the patient felt the movement only on the right hand. As soon as the stimulus was withdrawn from the right side, he felt the rubbing or scratching on the left side. Again, when the rubbing on the right side was resumed, the sensation due to the scratch stimulus on the left side disappeared. This could be demonstrated in repeated tests, probably because in stimulation by rubbing or scratching the adaptation time does not seem to be a factor. Graphesthesia, perception of the direction of drawn lines and point localization in areas on the left side, such as over the trunk, were inhibited by a painful stimulus on the right. The extinction of such perceptions, which involve spatial and temporal elements, was much more conspicuous than that of any of the simple modalities, such as painful tactile and thermal sensations.

Mentally, the patient was well oriented and clear. He made no errors in response to stimulations on the right side of his body. Here, graphesthetic perception and the simple modalities were not impaired when the left side was stimulated simultaneously. Mental distraction, such as engaging the patient in conversation, did not significantly alter the sensory responses to stimuli applied either to his left or to his right side. In contrast to this, however, when the patient was requested to concentrate on sensation on his left side during the double stimulation, he perceived only sensation on the right side. Special psychologic tests showed that the reaction time was normal and comprehension of instructions good. Performances in the vocabulary and information tests indicated a pretraumatic average intellectual level. This finding was in harmony with the educational history of two years of high school. Retentive capacity was found to be relatively defective, at borderline level, and a slightly poorer than average reasoning ability was shown. The conclusion was that moderate impairment in intellectual efficiency had followed the accident.

Case 2.—J. S., a Marine sergeant aged 28, was shot in the right side of the head while in battle. The bullet went through his helmet, striking the right parietal bone. He did not lose consciousness, but immediately after he was hit he felt his left hand become "dead." This condition lasted a week. A craniotomy was performed at a base hospital, where fragments of bone in the right parietal region were removed and the underlying cortex was found contused. The patient's condition improved. One month after the injury, he complained that the left hand felt "half asleep."

Physical examination revealed a pulsating wound, with a drain, in the right midparietal region.

Neurologic examination at that time showed complete astereognosis in the left hand and on the left side of the mouth, where he was unable to recognize a cigaret or a spoon held between the lips. Other sensory defects in the left hand were impairment of sense of position and recognition of initiation of movement in the fingers, defective two point discrimination and point localization, impairment of superficial and fine tactile sense and inability to judge weights. Pain and temperature senses appeared to be uninvolved when each side of the body or the extremities on the two sides were tested separately. In time the patient improved physically, and finally the drain was removed.

Four months after the injury, the neurologic status was practically the same as already noted, but the following additional changes were found: 1. Reduction of the sensory adaptation time. Although the pain sense seemed equal on the two sides when they were tested separately, the adaptation time for pain sense was reduced over the entire left side of the body, especially the hand. Three to five seconds after its application, the prick of a needle point became dull, changing to a pressure sensation, which, in turn, disappeared within seven to nine seconds. On the right side, the pain lingered for thirty-five to sixty-five seconds after the application of the stimulus. 2. Dulling or extinction of pain in the affected area as tested with the double stimulation method. Pain sense was found to be much reduced or obliterated on the left side during simultaneous, or double, stimulation. Moreover, although the patient clearly felt the prick of a pin in the left hand, this sensation was rapidly diminished or dulled when the right hand was stimulated simultaneously. In the various areas tested with the method of double stimulation, the dulling or extinction of cutaneous pain sensibility manifested itself on the left side of the body by the following phenomena: (*a*) further reduction in the adaptation time, so that one or two seconds after the application of the double stimulus the pain was replaced by pressure sensation and within three to five seconds the pressure sensation disappeared (compare with the effect of a single stimulus applied to the left side, as previously noted); (*b*) rise in the sensory threshold, so that the painful stimulus did not seem sharp, resulting in a sensation of pressure on the left side and in a sense of pain on the right side during double painful stimulation, or (*c*) total extinction of the sensation, so that the patient did not appreciate even the pressure of the applied stimulus of 25 Gm. with the needle point or realize that he was being touched at all on the left side. The type of inhibitory response on the left side seemed to vary in different parts of the body but was most pronounced in the left hand, especially when the stimulus on the right side was much stronger than that on the left.

An even more striking example of the dulling or extinction phenomenon was found in testing his tactile perception of letters, numbers or geometric figures drawn with a pencil on the skin (graphesthesia). A triangle, a circle, the letter *E* or the number *4* was well perceived when drawn individually on any part of the right or the left side of his body. However, when the left side was thus tested while the corresponding area on the right side was simultaneously pricked with a pin or gently rubbed or tickled with a pencil point, the patient was unable to detect the images drawn on the left side. Point localization was similarly influenced under the conditions of double stimulation. There was no difficulty in the graphesthetic perception or in point localization on the right side with the double stimulation method. The extinction phenomenon was much more conspicuous for graphesthesia than for sensations of pain, touch or temperature. Mixing or varying the stimuli did not materially interfere with the elicitation of the phenomenon.

Five months after the injury, the patient complained that when his left hand was out of sight he was unaware

7. It must be borne in mind that in testing for the vibration sense, tactile sensitivity is also being stimulated. It is possible, then, that the contact or weight, and not the vibration, of a tuning fork applied to the right wrist is responsible for the inhibition of painful or other stimuli applied simultaneously to the corresponding area on the left wrist.

of its presence and that he did not know its location. Occasionally, when his left hand dropped, he did not realize that it had done so. The position sense was slightly impaired in the fingers but in no other joints. The neurologic status remained unchanged. He continued to show the extinction and allied phenomena on his left side during double sensory stimulation. Adaptation time was notably reduced, and after-sensation was shortened or lost on the left side. Thus, he felt the sting or the tingling of a pinprick on the right side three seconds after the withdrawal of the stimulus, whereas there was momentary or no "after-sting" on the left side. Astereognosis in the left hand was still present. Despite the astereognosis, graphesthetic perception in the left hand was normal when tested for separately but was lost completely during double stimulation.

Other patients with lesions of the parietal cortex exhibited various stages and degrees of the sensory dulling or extinction phenomenon with the double stimulation method. In some patients there was only further reduction in the sensory adaptation time; in others there was transient dulling or raising of the sensory threshold, and in still others there was complete extinction of sensation, on the affected side. Most striking was the unilateral obscuration or abolition of graphesthetic perception with the double stimulation method. This was found in patients in whom no extinction phenomenon could be demonstrated for the simple modalities. Another conspicuous finding was that of obliteration of perception of a rubbing or scratching movement of a digit on the affected side during simultaneous stimulation on the two sides of the body.

The extinction phenomenon was best elicited when the stimuli were applied to corresponding points on the two sides of the body, such as the hands or the feet; but this, or the dulling of sensation, could be produced as well when the stimuli were applied to different parts of the body, e. g., the hand on one side and the foot on the other. The phenomenon was also manifest, but to a lesser extent, when the stimuli were applied at two points, such as the neck and the hand, on the affected side. In a few patients with hemiplegia, examination with the double stimulation method failed to disclose any dulling or extinction of sensation. These patients did not have demonstrable sensory defects. Evidently, not every one with a cerebral lesion exhibits the phenomenon.

### LESIONS OF THE SPINAL CORD

In a series of patients with injuries of the spinal cord who had the Brown-Séquard syndrome, there were a few in whom the sensory extinction phenomenon could be clearly demonstrated. The following case is an example.

CASE 3.—W. H. L., a 26 year old Marine corporal, sustained a gunshot wound in the neck while in combat in the South Pacific. He did not realize that he was injured until he found himself on the ground, with the delusion that his legs were disconnected from his body and hanging up in the air. For ten minutes he felt as though the legs were not his own. Finally, he realized that he was paralyzed and "numb" below the shoulders.

Examination revealed a small gunshot wound in the neck. The neck was swollen and discolored with blood. A roentgenogram showed a comminuted fracture of the laminas of the seventh cervical and first thoracic vertebrae on the right side. Neurologically, there was total loss of motor power and sensation below the sixth cervical dermatome bilaterally. One month after the injury, there was some restitution of function of the spinal cord. Motor power in the upper extremities and in the left foot began to return. Two months after the injury, the improvement was more apparent, and he showed signs of a lesion on the right side of the spinal cord with a Brown-Séquard syndrome.

Five months after the injury, he began to walk. Neurologic examination showed spastic weakness in both lower extremities, especially on the right side, and defective sensation on the left side below the seventh cervical dermatome, with the greatest involvement in the lumbar distribution. Deep pressure sense, point localization and graphesthetic perception were preserved throughout. Two point discrimination was much reduced on the left side. Although, with the ordinary method of sensory examination there was no apparent defect of pain sense on the right side of the body, the sensory adaptation times for pain and pressure sensation were decreased below the level of the seventh cervical dermatome. This reduction of adaptation time was the only clue to residual sensory defect in the formerly anesthetic area.

*Sensory Extinction Phenomena with Double Stimulation Method.*—On one examination the patient showed dulling of the pain sense in the left thigh and over the left side of the trunk. When asked what he felt, he stated, "It seems as if I don't pay attention to my left side when both sides are being stimulated." Subsequent examinations disclosed various areas of dulling of sensation on the left side. In the sacral dermatomes there were zones in which the cutaneous sensory extinction phenomenon for pain was present. Double stimulation over the buttocks with a needle point, using a 10 Gm. weight on the left side and a 25 Gm. weight on the right side, yielded sensation only on the right side, even though the patient attempted to concentrate on his left side. He was able to appreciate the pain and pressure of the point during single stimulation on the left side. On this side, the adaptation time for pain sensation with a 10 Gm. stimulus was five seconds, and that for pressure sensation, seventeen seconds. The painful sensation on the left buttock was dulled or abolished as soon as a stimulus was applied to the right buttock. The pain and pressure sensations in the left sacral dermatomes were also inhibited by a simultaneous stimulus applied to the right side of the neck and to a lesser extent, by one applied to the left side, as over the face or the upper part of the trunk. Interesting was the absence in the affected area of obscuration or extinction of graphesthesia, a phenomenon which is often associated with cerebral lesions. Other related phenomena noted on the left side during double stimulation were reduction of sensory adaptation time and raising of the sensory threshold. These were inconstant, but were significantly present on repeated occasions in the defective sensory areas.

This case is an example of cutaneous sensory extinction in a patient with a lesion of the spinal

cord and demonstrates that the phenomenon is not necessarily due to cerebral damage. In general, most of the patients in the series with lesions of the spinal cord did not manifest total extinction of sensation. A few showed transient and further reduction of the sensory adaptation time. Others manifested a rise in the sensory threshold in the affected area. Again, attention was evidently not a factor, for the patient was instructed, and he sincerely attempted, to concentrate on the side on which sensation was to be inhibited.

### LESIONS OF THE SPINAL ROOTS AND PERIPHERAL NERVES

Several patients with gunshot wounds of the cauda equina or the cervical roots were examined. The sensory defects found were of all degrees and often involved all modalities. Besides the sensory disturbances commonly noted, there were reduction of sensory adaptation time, decreased after-sensation and impairment of two point discrimination. Graphesthesia was not disturbed unless sensation was defective to such an extent that the patient was unable to detect even deep pressure. No extinction phenomena were elicited with the double stimulation method. In 2 patients with lesions of the cauda equina there appeared to be a further reduction in the sensory adaptation time in the affected area. This was the only evidence or suggestion of a form of sensory extinction in these patients. None of the patients with lesions of peripheral nerves showed any of the complete extinction phenomena. However, there were several patients with causalgia who demonstrated what seemed to be a corollary to the extinction phenomenon, namely, accentuation or intensification of the pain sense. Stimulation in the healthy areas precipitated or aggravated spontaneous pain in the causalgic, or painful, limb. A similar phenomenon has been observed in the opposite, normal limb, that is, perception of pain in the normal limb when the opposite affected limb was stimulated. This has been termed synesthesialgia by Wechsler.[8] It is related to allocheiria, in which the patient refers the tactile stimulus to a corresponding spot on the opposite limb. Wechsler stated that in some patients with "cerebral lesions, possibly also in cord disease and in hysteria," this type of sensory referral may be observed. The following cases are examples.

CASE 4.—D. H. C., a 28 year old Marine sergeant, was shot in the left arm. The arm jerked behind him, with the elbow bent, the wrist flexed sharply and the fingers contracted into his palm. There was no pain, and he thought for several moments that his arm had been shot off. There was brisk arterial bleeding. Sensation was lost below the wound, and the left upper extremity was paralyzed from the shoulder down. He was given emergency treatment. For three weeks, the motor and sensory defects remained unchanged except for a mild burning sensation in the skin across the metacarpal bones. One month after the injury, the median and ulnar nerves were explored for several inches and were found to be apparently intact. No lesion was noted except at a point where the brachial artery was constricted, apparently due to scarring. After this operation, there developed severe burning pain in the palm. The pain was worse with exposure to cold and was partially relieved by moistening the affected hand. The patient formed the habit of going to the water fountain every half-hour to wet both hands.

*Phenomenon of Intensification of Pain.*—The patient found relief from the spontaneous pain in the left hand when he wet the right hand. A drying or rubbing movement in the palm of the right hand produced a sharp exacerbation of the burning pain in the left palm. Thus, if he held a cup or if he gripped any other object with his right hand and this object happened to slip, or if the right hand moved across an object, an excruciating pain appeared in the left palm. A deep tickling of the ball of either foot also produced pain in the affected hand. However, application of a rubbing stimulus to other areas, such as the dorsum of the hand or the back of the neck, had no influence on the pain in the left hand. The patient also noted that emotional stress or the sound of a scraping noise, such as shuffling feet, or even the sight of a scratching movement evoked burning and sharp pain in the left palm. The most sensitive trigger point, however, was the middle of the right, or normal, palm. The patient had the symptoms of a typical major causalgia, with prominent vasomotor, sudomotor and trophic changes. The radial pulse was weak. There was marked hyperesthesia in the sensory distribution of the median and ulnar nerves. Pressure on the brachial artery brought relief of the spontaneous pain. Three months after the injury, the left median and ulnar nerves were surgically explored. Both nerves were found to be encased with scar tissue. The brachial artery was so scarred that it could not be identified. Some of the vessel strands were severed, and neurolysis of the scarred nerves was performed.

This operation was followed by notable relief of pain. Stimulation of the right side no longer influenced sensation over the left side. Trophic changes diminished. However, there were residual sensory defects in the distribution of the median, ulnar and medial antebrachial cutaneous nerves. There was still reduction of two point discrimination. The adaptation time for clear appreciation of a point was reduced. There was definite hyperpathia; the pinprick, although dull, seemed much more painful and spread over a greater area on the affected side than on the normal one. After-sensation was increased on the left side. There was no agraphesthesia and no sensory extinction phenomenon with the double method of stimulation. Graphesthetic perception was impaired in the left palm when the figure was drawn too rapidly. With slow drawing, the unpleasantness and spread of sensation produced by the stimulating object were not too great to interfere with the correct perception of the stimulus, so that the patient could recognize the figure written in

8. Wechsler, I. S.: Textbook of Clinical Neurology, Philadelphia, W. B. Saunders Company, 1943, p. 44.

his affected hand. After the last operation, the pain in the left palm was only occasionally intensified by a sudden scratching or scraping noise or by pronounced rubbing in the right palm. Scratching of the soles was no longer provocative.

Intramuscular injection of histamine acid phosphate, 2 mg., caused generalized redness and flushing of the face. With this injection there was excruciating pain in the left palm, which lasted twenty minutes. The pain due to injection of histamine was relieved by immersing the hand in cold water. Intramuscular injection of nicotinic acid, 30 mg., also produced a generalized flush, which spread from the head downward. The skin throughout the body felt hot and stinging, but there was no precipitation of pain in the left palm, as was found with histamine.

There were other patients with causalgia of the hand who showed this remarkable phenomenon, namely, accentuation of burning pain by application of a scraping stimulus to distant parts of the body, especially in the midportion of the opposite palm. In some patients the dry rubbing of any part of the body produced pain in the palm. In others the thought, sight or noise of a scratching, rubbing or scraping motion evoked severe tingling in the affected hand. There were also patients who had causalgia in the foot due to injury to the sciatic or the tibial nerve. In some of these unfortunate persons movement or scratching of the sole of the healthy foot increased the pain in the causalgic foot. The following case is an example.

CASE 5.—E. C. O., a 21 year old Marine sergeant, sustained shrapnel wounds in the right lower extremity, the left foot and the right eye. The right femur was fractured, and he had signs of a complete lesion of the right sciatic nerve. He was given appropriate treatment. Two days after the injury, a burning, sticking pain appeared in the right foot, especially in the toes. The right lower extremity was immobilized, but the pain in the toes persisted. Despite the lack of cutaneous sensation in this extremity, he had a "bursting" and "exploding" pain in the ankle, foot and toes. Five months later, he happened to run his hand over a scar on the lateral aspect of the right thigh. This produced severe tingling and burning in all the toes of the right foot. The sensation seemed to be limited to the plantar aspect of the toes. Later, he also noted that mild pressure on a scar situated in the right popliteal space produced tingling in all the toes of the right foot. Further studies showed that deep pressure, deep pain or a scratching movement over the plantar surface of the arch of the left foot evoked intense tingling and sharp, burning pain in all the toes of the right foot. The midportion of the plantar surface of the left, or normal, foot was the most sensitive area for the production of contralateral symptoms. Firm bending of all or of one toe on the left foot produced tingling and burning only in the right great toe. Rubbing or any other form of stimulation on the dorsum of the left foot, of the palms or any other part of the body except the trigger points previously described did not yield distant accentuation of burning in the right foot or toes. In fact, even rubbing or stimulation of the affected right foot was without effect. As already noted, there was complete loss of sensory and motor function of the right sciatic nerve. The right foot was dry, and electrical cutaneous resistance, as measured by the "neurodermometer," was very high, indicating sympathetic paralysis in the right foot and part of the leg (distribution of the sciatic nerve).

Emotionally, the patient was tense, irritable and hostile. He was puzzled by the fact that during his confinement to the hospital he had great urges for action and a desire to kill and to be exposed to danger. This aggression was expressed in dreams. The patient said that: "Occasionally, I have queer dreams in which my natural emotions seem to be suppressed. For example, I am in a pill box and am firing at the occupants, being frustrated in my attempts to kill them by such things as my rifle, which seemingly falls apart, or fails to function in some vital part. At the climax, I usually awaken, sometimes perspiring and breathing heavily, and with a great deal of pain in my foot."

The patient claimed that this was the only evidence of relationship between pain in the foot and emotional stress. Despite his tendency to suppress or inhibit his anger or anxiety, there was no accentuation or precipitation of the intense bursting or exploding variety of pain in his toes and foot, as evoked by stimulation of the trigger points. On one occasion the patient was so uncomfortable that he expressed a desire to have his right leg amputated, "since it was no good anyway."

This case illustrates that sensory stimulation in one area may intensify or precipitate spontaneous pain in the corresponding area on the opposite side of the body. The presence of severe burning pain in a foot which has no sensory, motor or sympathetic nerve supply is suggestive of phantom limb. Sometimes phantom limb may occur, without amputation, in cases of severe injury to the peripheral nerves in which there is loss of sensation in distal parts of the affected extremity.[9]

## COMMENT

The foregoing case reports are illustrative of a fairly large group.[10] From these observations, it is evident that sensation may be made extinct or pain may be intensified on one part of the body by a stimulus applied to another part of the body.

In the first group of cases, that of cutaneous sensory extinction, the phenomenon was demonstrable in an area deficient in sensation when this and a normal area of the skin were stimulated simultaneously. The phenomenon is most often encountered in cases of cerebral lesions, infrequently in cases of disease of the spinal cord and, except for slight dulling of sensation, practically never in cases of peripheral nerve defects. The sensory extinction phenomenon may manifest itself in varying degrees, from a slight reduction in sensory adaptation time, or rise in the

9. Riddoch, G.: Phantom Limbs and Body Shape, Brain **64**:197-222, 1941.

10. Because of military regulations, detailed statistics cannot be presented at this time.

sensory threshold, with dulling of the pain sense, to complete extinction of sensibility. The sensibility which seems to be most vulnerable and becomes readily extinct on the affected side during double, or simultaneous, stimulation is graphesthesia, a perceptual process which requires temporal and spatial sensory integration at the cortical level. The least vulnerable has been found to be the sense of vibration, which is known to be appreciated at the thalamic, and not at the cortical, sensory level.[11] On the basis of these observations, it would seem that the sensory extinction and allied phenomena take place in the cerebral cortex and are particularly evident when one cortex is diseased. However, since the phenomena have been elicited in patients with lesions at lower levels of the nervous system, it is obvious that they are not entirely dependent on the structural condition of the sensory cortex.

There must be physiologic, rather than anatomic, elements to account for the fact that tactual stimulation of one area influences (inhibits) the corresponding area on the other side of the body. A physiologic or psychologic mechanism which is known to operate in the normal subject is rivalry between the sensations arising from the two sides or different parts of the body. Heyman's law states that simultaneous stimuli inhibit each other.[12] Naturally, if there is a difference between the perception of the two applied stimuli, the stronger sensation will have a more powerful inhibitory effect on the weaker than will the latter on the former. Sensations between the two sides are in constant competition with each other, and, as noted in the pathologic states described in the first 3 case reports, the stronger the sensation is on one side, the less the patient perceives on the weak side.

The principle of sensory dominance can be demonstrated to a certain extent in the normal subject, as when a strong painful stimulus at one point inhibits pain at another. The relief of pain obtained with the method of counter-irritation is based on this principle. But why sensory extinction is so apparent in persons with cerebral lesions and less evident in those with lesions at lower levels or in the normal subject is difficult to explain. The factor of "attention" does not seem to play an important role, for, as has repeatedly been described in the case reports, the focusing of the patient's attention on the affected side did not appreciably influence the extinction or obscuration phenomenon. Occasionally, the patient complained that the stronger sensation distracted him from his ability to perceive sensation on the opposite side, but this evidently was not due to inattention, for the patient concentrated on the stimulus applied to the affected side.[13]

A theory which may account for the occurrence of the phenomenon in patients with cerebral lesions is that of Goldstein,[14] to the effect that the available nerve energy, which is constant, is utilized better and to a greater extent by the normal cortex, so that an insufficient quantity is left for the use of the diseased cortex in effecting a performance. Still, this hypothesis does not explain why some patients with sensory cortical lesions do and others do not show the extinction or the allied phenomena, and why some patients with lesions in the spinal cord manifest the phenomenon. Emotional factors, such as suggestion or hysterical reactions, are possibilities to be considered. In fact, in a patient with a hysterical hemisensory syndrome, the phenomenon of extinction of a dull sensation was elicited. This, however, was inconstant, and the sensory distribution which he manifested had no known anatomic pattern.

Interesting and significant is the prominence of the extinction or dulling of sensation when simultaneous stimulations are made in corresponding areas on the two sides of the body, such as the two hands, arms, thighs, legs or clavicular regions. The sensory phenomena are not so apparent when the arm on one side and the trunk or the leg on the other or on the same side are stimulated simultaneously. In a patient with a lesion of the spinal cord, simultaneous stimulation of two different areas on the same side produced some inhibition in the hypalgesic zone, thus suggesting that the inhibition may be ipsilateral. Although the phenomenon could be elicited by application of two stimuli to any part of the body, the best cutaneous sensory extinction can be demonstrated when two corresponding points, on opposite sides of the body, are stimulated simultaneously.

11. Weinstein, E. A., and Bender, M. B.: Dissociation of Deep Sensibility at Different Levels of the Central Nervous System, Arch. Neurol. & Psychiat. **43**:488 (March) 1940.

12. Cited by Guilford, J. P.: Fluctuation of Attention with Weak Visual Stimuli, Am. J. Psychol. **38**:534, 1926.

13. It is well known that distraction, attitude and suggestion may modify the threshold and the manner of reaction to pain (Hardy, J. D.; Wolff, H. G., and Goodell, H.: The Pain Threshold in Man, A. Research Nerv. & Ment. Dis., Proc. [1942] **23**:1, 1943), but how and where these modifications take place is not clearly understood.

14. Goldstein, K., in discussion on Bender and Furlow,[3] and personal communications to the author.

In the second group of cases, spontaneous pain could be precipitated or aggravated by scratching or dry rubbing in another part of the body. The topographic factor seemed also to be prominent in this group. In case 4, it was the cutaneous stimuli coming, chiefly, from the right, or normal, palm, such as dry rubbing or scratching, which influenced sensation (precipitation of spontaneous pain) in the opposite, or causalgic, palm. In case 5, deep pressure, rubbing or painful stimuli in the left, or normal, foot caused pain and burning in the causalgic toes on the right side.

The phenomena of contralateral sensory extinction or dulling, contralateral intensification of pain, synesthesialgia and allocheiria all show the functional and topographic relationship between the sensations on the two sides of the body. At what level in the nervous system this relationship, inhibition of a painful stimulus or precipitation of pain, occurs is difficult to ascertain. It may be in the spinal cord, the thalamus or the cortex, but perhaps largely in the cortex. Livingston,[15] in his monograph on pain mechanism, stated that he had personally observed some 35 cases in which a long-established pain syndrome in one limb spread to involve the contralateral limb in the same distribution. This he called the "mirror image phenomenon." He also cited Weir Mitchell as having frequently made similar observations. Mitchell [16] described a case in which dry rubbing on or use of the normal palm caused pain in the causalgic palm. As an explanation of the spread of pain to the opposite, or even to the same, side of the body, Livingston [15] stated that some "dynamic process has been initiated within the spinal cord that may persist after the original stimulus is withdrawn," and "that the original initiative lesion initiates some changes in the activities of the regulatory centers of the central nervous system that eventually acquires a self-sustaining momentum." In other words, the induction of sensory disturbances on the side opposite the original cutaneous focus is due to some physiologic, or perhaps psychologic, change in the central regulating or integrating levels of sensation. Of course, this is pure speculation, but there must be some sort of sensitization in the cortex or the thalamus to explain the increase in pain.[17]

These clinical observations recall the experiments of Dusser de Barenne [2] in which painting a few square millimeters of the cortical arm area on one side with strychnine produced hyperalgesia in both arms in the monkey. These experiments with strychnine suggest that the precipitation of pain in the distribution of a very sensitive nerve on stimulating the corresponding cutaneous area of the opposite hand or foot in man is due to some change in the cortex, which has been sensitized by a psychic or physiologic agent or through some other mechanism. Why in some subjects a rubbing or scratching motion is the only type of stimulus which accentuates pain on the opposite side is not clearly understood, unless a moving stimulus is more effective than a static tactile or thermal stimulus, to which the organism readily adapts. In some cases, deep pressure and painful stimuli, especially when applied repeatedly, precipitate burning or boring pain in the affected hand or foot. In others, even the sight, hearing or thought of a scratching movement will produce pain, thus indicating that the reflex response to pain goes through a cerebral or cortical arc. There is also a possibility that this reflex response of pain in the affected palm or foot on stimulation of the normal area occurs at a spinal level by way of the pain fibers which are transmitted by the vascular tree.[18] Thus, a scratching or scraping movement produces a generalized vasomotor response, which is bound to include the vessels in the affected extremity. In turn, the vasomotor reaction in a hypersensitive area may precipitate a severe burning or tingling pain by stimulating the sensitized pain fibers in the blood vessels.

When all the facts are compiled, it appears that the unilateral sensory extinction phenomenon with the method of double stimulation and the precipitation of contralateral causalgic pain with a unilateral rubbing or scratching stimulus are closely related and are, respectively, the inhibitory and the excitatory phase of the same phenomenon. The physiologic or psychologic interaction of these phases most probably occurs in the cerebral cortex, although it may also

15. Livingston, W. K.: Pain Mechanisms, New York, The Macmillan Company, 1943.

16. Mitchell, S. W.: Injuries of Nerves and Their Consequences, Philadelphia, J. B. Lippincott & Company, 1872.

17. A similar mechanism has been postulated in the mysterious syndrome of phantom limb. The sensation of the phantom limb has been attributed by some authors to sensitization in the parietal cortex, with a "cortical engraving." Based on this theory de Gutiérrez-Mahoney (de Gutiérrez-Mahoney, C. G.: The Treatment of Painful Phantom Limb by Removal of Post-Central Cortex, J. Neurosurg. **1**:156 [March] 1944) excised the parietal cortex and thus successfully abolished the painful "phantom limb" on the opposite side.

18. Foerster, O.; Altenburger, H., and Kroll, F. W.: Ueber die Beziehungen des vegetativen Nervensystems zur Sensibilität, Ztschr. f. d. ges. Neurol. u. Psychiat. **121**:139, 1929.

take place at lower integrating sensory levels. In either case, whether there is inhibition or excitation of pain, these observations reveal a bilateral functional relationship of the cortex to sensation on the two sides of the body and lend support to Dusser de Barenne's conclusions drawn from animal experiments, that each sensory cortex may influence sensation on both sides of the body.

## SUMMARY AND CONCLUSIONS

In the cases described, dulling or extinction of cutaneous sensation occurred in an affected area, when this and a normal area, usually the corresponding one on the opposite side of the body, were stimulated simultaneously. When the affected area alone was stimulated, it might be fairly sentient. In other cases, pain was precipitated or spontaneous pain aggravated in a causalgic limb when the opposite hand or foot or some distant part of the body was stimulated.

The cutaneous sensory extinction and the precipitation of pain by stimuli from the opposite side of the body are probably related, one being the positive and the other the negative phase of the same phenomenon. It is hypothesized that both phases of the phenomenon take place in the sensory cortex and that there is a bilateral functional relationship between the sensations of the two sides of the body.

# MAN'S FRONTAL LOBES

## A CRITICAL REVIEW

D. O. HEBB, PH.D*

ORANGE PARK, FLA.

Examination of the current literature concerning the frontal lobes reveals an almost universal belief that surgical removals from this area must produce serious psychologic defects. The evidence on which the belief is founded, however, is not nearly so satisfactory as one might suppose. In this paper I propose to review and evaluate the published reports which attempt to analyze the functions of the frontal lobes on the basis of neurosurgical material. In the review, emphasis is laid on problems of method which are common to any such analysis, whatever region of the brain may be concerned.

The occasion for a reevaluation of theories concerned with the frontal lobes was a fortunate opportunity to observe the social adjustment of K. M., a patient of Dr. Wilder Penfield's, six years after a partial bilateral frontal lobectomy (Hebb and Penfield,[1] 1940). The patient's excellent recovery showed that a large bilateral removal is not always followed by gross defects of behavior. The differences between this case and others, in which serious maladjustments have been found, demanded explanation. What factors determine whether the outcome of operation will be good or bad? The answer to this question is as important for therapy as for psychologic theory. Accordingly, although the present discussion deals throughout with the theoretic problem of localization of function, its conclusions also have a practical significance for the clinician.

### PERSONAL ADJUSTMENT SIX YEARS AFTER BILATERAL "LOBECTOMY"

The preceding report on K. M. (Hebb and Penfield[1]) was written a year after operation. At the age of 16 years a fracture in the frontal area destroyed both frontal poles of the brain. For ten years increasingly severe epileptic attacks made the patient an irresponsible charge to his parents. Between outright convulsions he was childish, violent, stubborn and destructive, with gross defects of memory and ordinary judgment. There were periods when he was normally responsive and restrained, but he was not himself aware of the transition to one of his violent and stubborn moods. Others could detect it only by the actual change of behavior. He would go outdoors in the winter weather of Nova Scotia without warm clothing, for example; and as to persuading him to act differently, "you might as well talk to a post." He might set out for the grocer's or to mail a letter, and return late at night without having completed his errand. He might walk into any house he saw and destroy anything in his way. Since he was strong and big, the neighbors were terrified of him, and even when he was not in one of his violent moods he sometimes took a malicious pleasure in pretending that he was, in order to frighten others.

Now, six years after operation, his relatives are still sure, as they were a year after the lobectomy, that he has become normal in every way. The independent testimony of three residents of the village—taxi driver, storekeeper and waitress—is that there is nothing wrong with K. M.'s behavior now and that he is one of the most popular persons in the village. The malicious joking has stopped with the improvement in other behavior.

In February 1942 he joined the Canadian army. This was at a time when Canadian headquarters in England had been sending home psychoneurotic men and misfits for a year or more. Every commanding officer in Canada was under pressure to find and weed out unsatisfactory personnel, and efforts were made to detect such men early in training. Recruits at that time did not have psychiatric examination as a routine, but there was a directorate of personnel selection, staffed mainly with psychologists, to deal with misfits. This mechanism for handling the maladjusted or mentally incompetent as they were discovered in training was freely used.

* Research Fellow, Harvard University.

From the Yerkes Laboratories of Primate Biology, Inc.

1. Hebb, D. O., and Penfield, W.: Human Behavior After Extensive Bilateral Removal from the Frontal Lobes, Arch. Neurol. & Psychiat. **44**:421-438 (Aug.) 1940.

Nevertheless, K. M. was in the army for ten months, and had been sent overseas, before an epileptic attack, precipitated by hard labor, brought him to the medical officer's attention, when he was discharged.

He had apparently had no other attacks since his first postoperative year (when he twice stopped taking phenobarbital, 1 grain [0.065 Gm.] a day, and each time had an attack). Since the attack in England he has had three other seizures in a year and a half. According to the patient, these occurred in spite of his taking the phenobarbital as usual. The recent convulsions have always been at night, during sleep. He has also on perhaps five or six occasions had a slight and transient state of confusion as he was about to fall asleep.

K. M. has no trade or special skill, but in a wartime shortage of labor he has no trouble in finding jobs, which he does himself, without any family guidance. He has in fact had half a dozen jobs since his discharge from the army. He works in a neighboring town (population about 4,000), where he is not especially known. He is liked by his employers, as far as can be ascertained, and apparently other employers entice him away with offers of better working conditions, and so on. When his family was first interviewed, with the object of arranging a later interview with K. M. himself, he had just given two weeks' notice to his employer. He worked those two weeks as usual and then quit for what were undoubtedly better working conditions. It seemed, however, that his brother was not pleased with the frequent changes, and in conversation K. M. showed no great concern about finding a job with permanence or future. He apparently saved enough from each week's pay so that he always had money when he needed it; but nothing more could be discovered about his spending habits, and he probably is making no effort to save for the future. However, his good social relationships and his provision for at least a few days ahead show no sign of the "lack of foresight" by which Freeman and Watts [2] interpret their patients' social errors. The amount of foresight needed to avoid the tactlessness described by Freeman and Watts is at most of the order of minutes; K. M.'s foresight certainly anticipates his own actions days or weeks in the future, and possibly to more remote periods. While the examiner was trying to find out whether K. M. was making any effort to "better" himself, the latter mentioned a half-formed intention of going to Toronto, about 1,000 miles (1,600 kilometers) away. This confirms the impression that K. M. was rather too ready to shift jobs, since he had no prospects of a particular kind of work when he got to Toronto, but it also suggests an unexpected degree of initiative.

The patient was tested with Goldstein's [3] figures, to be copied with match sticks from memory, and with single and double alternation and delayed response problems. No suggestion of defect was discovered, a result which perhaps might have been predicted from the patient's earlier performance on a varied battery of other tests (Hebb and Penfield [1]).

The conditions of testing delayed response were crude and did not duplicate those of Jacobsen [4] or Malmo.[5] However, these authors generalized their results, reasonably enough, beyond the actual laboratory conditions in which they were obtained, and it may be said that the human patient with bilateral loss of the frontal association areas is capable of a kind of performance which the lower primates with similar lesions cannot carry out.

There is no reason to treat such a result as puzzling or improbable. Even if the frontal lobe in man has the same functions as that in the lower primates, the human brain as a whole is certainly more developed and may be capable of solving delayed response problems by more than one mechanism. The capacity for speech in itself provides a mode of solution which the monkey does not have. Supposing, then, that the human frontal lobe contains a mechanism of delayed response, the speech area and the rest of the brain may provide another. If so, one would find no evident loss of delayed response in a man with the same injury to the frontal lobe which prevents delayed response in monkeys.

## EXPLANATION OF DISCREPANCY BETWEEN K. M.'S CASE AND OTHER CLINICAL CASES

K. M.'s lack of gross defect is unexpected, to say the least. Other cases of large bilateral surgical destruction of frontal areas have been

2. Freeman, W., and Watts, J. W.: Psychosurgery: Intelligence, Emotion and Social Behavior Following Prefrontal Lobotomy for Mental Disorders, Springfield, Ill., Charles C Thomas, Publisher, 1942.

3. Goldstein, K., and Katz, S. E.: The Psychopathology of Pick's Disease, Arch. Neurol. & Psychiat. **38**:473-490 (Sept.) 1937.

4. Jacobsen, C. F.: Studies of Cerebral Functions in Primates: I. The Functions of the Frontal Association Areas in Monkeys, Comparative Psychology Monographs, Baltimore, Johns Hopkins Press, 1936, vol. 13, no. 3, pp. 3-60.

5. Malmo, R. B.: Interference Factors in Delayed Response in Monkeys After Removal of Frontal Lobes, J. Neurophysiol. **5**:295-308, 1942.

reported, particularly by Brickner,[6] Nichols and Hunt [7] and Mixter, Tillotson and Wies.[8] All 3 patients in these reports have had to have continued care and detention, and it is assumed, by some of these authors and by others, that the reason for the social incapacity is to be found in the surgical loss of frontal lobe tissue.

The patient operated on by Dr. Penfield presents an entirely different picture. No psychologic defects can be definitely demonstrated. He is, indeed, a strikingly easy-going, carefree fellow, and his lack of concern for the distant future could be due to the cerebral excision. But to prove that this is so is another matter. One can find plenty of normal persons with no more care for the morrow, and certainly with less concern about giving their employers notice when they are going to change jobs. Among patients who have recovered from long hospitalization for tuberculosis there is not infrequently the same easy feeling that tomorrow must be left to care for itself. It is hard in this case to evaluate the psychologic effect of ten years of severe epilepsy and that of the postoperative eighteen months or so of convalescence before the patient was permitted to work. The patient's attitude is consistent with the idea that lesions of the frontal lobe affect initiative and planning (Penfield and Evans [9]), but proof of the hypothesis is still difficult.

Thus no defect of social adjustment or of intellectual capacity in K. M. is clearly shown. How is one to interpret the glaring differences between his case and the cases reported by other authors, in which social defects were so obvious? The reader may feel, perhaps, that the psychologic search for defects in K. M. was not competent or not thorough. Must he not have the symptoms found in other patients? But K. M. was able to join the army and remain unnoticed until he had a fit, whereas the patients reported on by other authors have had to be detained and cared for. K. M., therefore, has not the main symptoms presented by other patients. If it is still believed that the examination by laboratory methods was not thorough enough to reveal subtle defects, his grossly superior social adjustment is still to be explained.

Another possible explanation of the differences between K. M.'s case and other cases might be a considerable individual variability in function of the frontal lobe. K. M.'s lack of the expected deterioration could be due to an atypical cerebral organization. This possibility cannot be ruled out; one can only say that the reverse assumption has been made by every student of cerebral function.

However, before one accepts the assumption of such great individual variability, one must examine a third possibility. This is suggested by the fact that K. M.'s operation was for the removal of a specific area of scarring, not for tumor (as in the cases of Brickner,[6] Nichols and Hunt [7] and Karnosh [10]) or for the removal of areas of atrophy with a possibly indeterminate extent (Mixter, Tillotson and Wies [8]). The removal of K. M.'s scar was so done as to minimize further scar formation or a residue of pathologically changed tissue. The possibility exists, therefore, that K. M.'s case is a rare one, in which the effect of surgical removal of frontal lobe tissue is not obscured by the presence of further lesions. There is, in fact, positive evidence in some of the cases reported by other authors that they were not dealing with uncomplicated surgical lesions. The deterioration they describe may have been due to pathologic complication and not to the surgical lesion at all.

The clinical analysis of cerebral function is not so easy as it has sometimes appeared, and I must now draw attention to its difficulties before returning to the published case reports and their divergent conclusions. Although the following discussion (of anatomic and pathologic data and the difficulties of getting normal control data) is in the main concerned with studies of the frontal lobe, the methodologic difficulties it deals with apply in general to any analysis of the effect of surgical lesions, and not to study of a particular part of the brain.

## ANATOMIC AND PATHOLOGIC SOURCES OF ERROR

In operations on the frontal lobe there is frequently a deliberately planned and radical removal of cerebral tissue. At first sight, the result is made to order for the analysis of function of this area. But all is not so simple.

*Anatomic Data.*—The special value of a surgical lesion of the brain is that it may have

6. Brickner, R. M.: The Intellectual Functions of the Frontal Lobes: A Study Based upon Observation of a Man After Partial Bilateral Frontal Lobectomy, New York, The Macmillan Company, 1936.

7. Nichols, I., and Hunt, J. M.: A Case of Partial Bilateral Frontal Lobectomy: A Psychopathological Study, Am. J. Psychiat. **96**:1063-1083, 1940.

8. Mixter, W. J.; Tillotson, K. J., and Wies, D.: Reports of Partial Frontal Lobectomy and Frontal Lobotomy Performed on Three Patients: One Chronic Epileptic and Two Cases of Chronic Agitated Depression, Psychosom. Med. **3**:26-37, 1941.

9. Penfield, W., and Evans, J.: The Frontal Lobe in Man: A Clinical Study of Maximum Removals, Brain **58**:115-133, 1935.

10. Karnosh, L. J.: The Clinical Aspects of Frontal Lobe Disease, J. Indiana M. A. **28**:568-572, 1935.

definite limits and destroy all tissue within its boundaries while the rest of the brain remains intact. If these conditions do not hold, however, there is no superior scientific value of the surgical lesion over pathologic lesions, and localization of function is no more possible in such a case than in a case of brain tumor in which no operation is done. The confusion of early theories, before brain surgery was common, shows clearly the need of basing localization of function on the results of well defined lesions. One might think that surgical operations would provide many such lesions, but the fact is that cases are rare in which one can either (*a*) say definitely what tissue is removed or (*b*) have any assurance that the surgical lesion alone can be taken into account. Clearly, if symptoms are to be ascribed to the removal of tissue from the frontal pole, one must be sure that the removal constitutes the only lesion. But the good cases for psychologic study do not come to autopsy, and without autopsy one cannot be sure that this is true. In the great majority of cases, in fact, it is quite untrue.

Physiologists and psychologists have long recognized in animal experimentation that the only good source of information about the nature of a cerebral lesion is the histologic study of the brain after necropsy. One must usually get along without necropsy data in the clinical study, but this does not mean that the information is less needed. The neat diagrams, published to show just where a surgical excision occurred in clinical cases, are quite misleading in their appearance of accuracy. It is difficult, sometimes impossible, to identify gyri at operation. When growth of a tumor has distorted the brain, any claim to precise localization is nonsense. Further, there may be destruction at a distance, due to tumor growth and compression of the whole brain; and there may be other pathologic changes which the surgeon can recognize, but cannot remove, if they lie within the specialized motor or speech areas or at the base of the brain. For various reasons, the complications of clinical operations on the brain are much more frequent than are those in animal experiments. Little weight would be given to localization of function established by animal experimentation without necropsy data; how can one give more to a clinical study, in which the data are just as necessary?

Of course, some information about the function of the human brain is better than none. The moral is not to abstain from studying clinical material until the perfect case is found, but to regard fallible data as fallible, to make every effort to get as good cases as possible and to put most weight on the cases in which anatomic data are most complete and trustworthy. One must not lump together all cases in which the frontal lobes have been touched by a surgeon and then treat them as a homogeneous group.

It has been pointed out elsewhere (Hebb[11]) that a negative conclusion—the conclusion that a given function is not dependent on a certain cortical region—can often be made with more security than a positive conclusion, since it is easier to determine that a specific area has been removed without producing mental symptoms than that symptoms accompany destruction in one area only. It is well to keep in mind these two aspects of the localization of function. A given hypothesis can be refuted conclusively but can be established only with great difficulty.

*Pathologic Disturbances.*—So much for the outright destruction of tissue. I come now to the question of the physiologic changes which occur in an area of incomplete destruction. One reason, no doubt, that accompanying pathologic lesions are usually forgotten in selecting cases for study, and in the interpretation of symptoms, is that they tend often to be small and may seem negligible as compared with a large surgical removal. But this assumption overlooks an important fact. The small and diffuse region of partial necrosis can have a greater effect in the production of symptoms than a larger area of complete destruction and cleancut removal of tissue.

Electrophysiologic studies provide a rationale for this otherwise anomalous state of affairs. It is known that spontaneous rhythmic neural activity is induced or modified by changes in the cell mediums, and therefore by changes in the chemical constitution of the cell itself (Fulton[12]). Deficiency of blood supply in the frontier zone of a scar (Penfield and Humphreys[13]) or in an area of increased pressure due to the presence of a cerebral tumor could, obviously, produce such chemical changes. The chromatolysis in an area of incomplete destruction also implies a chemical change within the cells. This, in turn, means a change in the pattern of cellular action. Such a change might occur in many ways, but there is at least one way which would adversely affect function in the rest of the brain. Electroencephalo-

11. Hebb, D. O.: Human Intelligence After Removal of Cerebral Tissue from the Right Frontal Lobe, J. Gen. Psychol. **25**:257-265, 1941.

12. Fulton, J. F.: The Central Nervous System, in Luck, J. M., and Hall, V. E.: Annual Review of Physiology, Stanford University, Calif., Annual Reviews, Inc., 1940, vol. 2, pp. 243-262.

13. Penfield, W., and Humphreys, S.: Epileptogenic Lesions of the Brain: A Histologic Study, Arch. Neurol. & Psychiat. **43**:240-261 (Feb.) 1940.

graphic studies in general show an inverse relation between integrated mental function and the synchronous action of individual cells (hypersynchrony) which is implied by large potentials (Jasper, Kershman and Elvidge [14]). In an area of injury, the electroencephalogram reveals a pronounced increase of synchronous activity appearing as slow waves or spikes, which must have a tendency to act as pacemaker and increase synchronization in neighboring tissue. The perfect example of this is supplied by Dr. Herbert Jasper,[15] who observed a patient with periods of transient aphasia coinciding with the discharge of large potentials from the speech area: Synchronization of cellular rhythm and apparent hyperactivity obliterated normal function instead of increasing it. If hypersynchrony is indeed the negation of integrated function, the effect of neural processes within an area of injury must at times be deleterious in their relation to processes elsewhere.

This reference to intercellular relations is rationalization rather than an explanation of observed clinical phenomena, for the course of events is in part inferred from these phenomena; but it is worth showing that the deleterious effect of pathologic processes, and an actual improvement of mental level following the extirpation of the tissue concerned, is not out of accord with physiologic theory. It had often been suspected that pathologically affected tissue, as such, could interfere with normal cerebral function; but the idea was not given great weight, apparently because there was no rational basis for it and the evidence was not overly clear. The first convincing evidence came only with cases of clean surgical extirpation from the frontal lobes (Jefferson [16]), evidence which was strengthened by drawing attention to the meaning of the concomitant electrical phenomena (Hebb [17]). The same conclusion was arrived at, apparently independently, by Stookey, Scarff and Teitelbaum.[18]

Finally, conclusive evidence that pathologic changes not productive of pressure on the rest of the brain could nevertheless have a detrimental effect on its activity was provided by 2 cases in which improvement followed bilateral removal of an area of atrophy or of scar tissue (Mixter, Tillotson and Wies [8]; Hebb and Penfield [1]) from the frontal lobe. In these 2 cases the patients had epilepsy; but the argument of Jefferson [16] and of Stookey, Scarff and Teitelbaum [18] shows that the same principle may apply in cases of brain tumor.

The importance of the careful removal of pathologic tissue and the necessity of avoiding postoperative scar formation have been stressed by Penfield.[19] His argument, based primarily on neuropathologic data, is strongly supported by the excellent psychologic and behavioral status of patients following operation in which the degree of further scar formation is minimized. In appraising the effect of pathologic destruction as a complication of surgical operation, therefore, one must take account of the physiologic disturbance in cells whose function has been disordered, as well as of the total loss of cells. The pathologic lesion may be small or diffuse, but its size or concentration is not a safe guide to its importance in producing symptoms. It seems, then, that evidence concerning the suitability of a case for the study of localization of function must include electroencephalographic data. The electroencephalographic evidence is as necessary as are anatomic data in the interpretation of symptoms. It is not suggested that the electroencephalogram is infallible; but it is the only index of the physiologic status of cerebral tissue in the living patient, and as such it becomes of the first importance.

It is particularly important in cases of tumor to have good pneumoencephalographic and electroencephalographic data. After removal of a tumor there are often indications of widespread atrophy. The interpretation of such evidence is sometimes disputed, and signs of atrophy may be misleading. Nevertheless there seems to be no doubt that the growth of a large tumor is frequently accompanied by pathologic changes in the rest of the brain. The most likely factor is pressure, but what the cause may be is not important for the present discussion. Also, it may be doubtful whether pressure atrophy necessarily produces psychologic symptoms; but when symptoms are present, the presence of atrophy cannot be disregarded. When a large tumor has been removed, therefore, one must be cautious in at

14. Jasper, H. H.; Kershman, J., and Elvidge, A.: Electroencephalographic Studies of Injury to the Head, Arch. Neurol. & Psychiat. **44**:328-350 (Aug.) 1940.

15. Personal communication to the author. Dr. Jasper points out that hypersynchrony per se is not necessarily what prevents normal function, since the refractory states of the tissue must also be taken into account. What is important for the present discussion is the empiric fact that integrated function vanishes as synchronous activity increases.

16. Jefferson, G.: Removal of Right or Left Frontal Lobes in Man, Brit. M. J. **2**:199-206, 1937.

17. Hebb, D. O.: Intelligence in Man After Large Removals of Cerebral Tissue: Report of Four Left Frontal Lobe Cases, J. Gen. Psychol. **21**:73-87, 1939.

18. Stookey, B.; Scarff, J., and Teitelbaum, M.: Frontal Lobectomy in the Treatment of Brain Tumors, Ann. Surg. **113**:161-169, 1941.

19. Penfield, W.: Epilepsy and Surgical Therapy Arch. Neurol. & Psychiat. **36**:449-484 (Sept.) 1936.

tributing psychologic symptoms to the surgical excision alone (Dandy [20]).

*Anatomic and Pathologic Conclusions.*—From all these considerations, several conclusions may be drawn concerning the case material that is suitable for the localization of function.

1. Cases of injury to the brain—atrophic, neoplastic or traumatic—for which operation is not performed cannot be used, with possible rare exceptions. Neither the minimal nor the maximal extent of outright destruction can be determined, nor can the probable effect of physiologic dysfunction be evaluated.

2. Cases in which intracranial tumor has been removed are rarely satisfactory. In some instances it may be possible to determine the minimal extent of surgical destruction; if so, negative conclusions may be justified. Positive conclusions can be established only if the maximal possible destruction is known and is limited to a specific area and if physiologic dysfunction is ruled out. These conditions are practically never met in operations on large tumors.

3. In practice, surgical procedures are always more or less complicated by pathologic changes in the part of the brain that remains after operation, and one has no way at present of knowing the effect of such changes in the individual case. Of two cases in which identical surgical removals have been made, but with pathologic complications of varying effects, the one in which the fewer symptoms occur is the one which most clearly shows the effect of the surgical removal alone. Consequently, this principle may be stated: The case in which the fewest symptoms follow a known surgical removal is likely to be the one in which the truest picture of the effect, or lack of effect, of the removal is given, and for the localization of function the most weight must always be given to such a case.

## MISUSE OR LACK OF NORMAL CONTROL DATA

If some of the statements about anatomic data seem obvious, just as obvious are certain facts about normal control data, which nevertheless need to be emphasized again. One cannot use school children as normal control subjects for adults, or college students for the middle-aged, or academic and clerical workers for farm populations. Yet when normal control subjects are used at all, it is frequently in just such a way.

It is not generally appreciated that an adequate normal control group is extremely hard to obtain in clinical studies of adults. Intelligence test norms are data from a normal control group and may be used as such as long as the clinical subject comes from the same population. Unfortunately, the test data are usually obtained from school children and are not applicable to adults. To some workers, apparently, this appears to be a trivial point—legitimate, but unimportant. On the contrary, a review of the published cases indicates that failure to find adequate normal controls has repeatedly led to serious error.

An intelligence test which has been standardized with adult subjects is the Wechsler-Bellevue scale.[21] At first glance, this test seems to supply the normal control data that are needed for analysis of adult clinical performance. But there are still difficulties, such as the low reliability of the subtests of the scale, which makes it practically useless for a small group of subjects, and the limited range of material which the test provides. Another difficulty is less obvious, but greater. Wechsler has provided no information whatever about the original selection of subjects. Nearly 2,000 subjects were tested in the first place; and the choice of records from this pool, to determine test norms, was a model of the sampling process. But any one who has tried to obtain the consent of subjects chosen at random from the general population, even when they are out of work and are to be paid for being tested, knows how difficult it is to avoid a high percentage of refusals. In some circumstances refusals can result in a marked bias. The utmost care, diplomacy and patience must be continually exercised with adult subjects to obtain their original consent and to have them complete the testing process. It is not at all clear how the extremely large number of cases in Wechsler's original pool could have been obtained without the danger of bias running through the whole group. If there is a bias, multiplication of cases will not offset it in the least, and nothing in Wechsler's later procedure would eliminate it. It is known that the range of ability within any one occupational group is great, and stratification by occupation would not eliminate a selection that might have affected every stratum in the same way. Before the test norms can be used as normal control data, more information is necessary about the original selection of subjects and the way in which so many adults, supposedly chosen at random, were induced to cooperate in the study.

As to the use of child norms with adults, an illustration will show how real the dangers are.

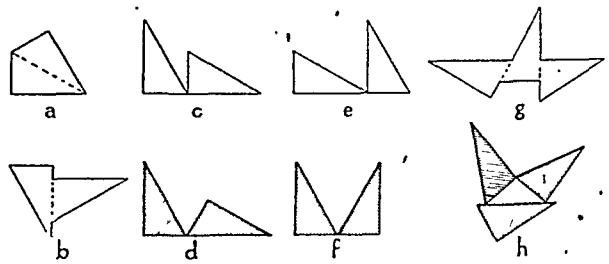
20. Dandy, W. E.: Physiologic Studies Following Extirpation of the Right Cerebral Hemisphere in Man, Bull. Johns Hopkins Hosp. **53**:31-51, 1933.

21. Wechsler, D.: The Measurement of Adult Intelligence, Baltimore, Williams & Wilkins Company, 1939.

Nichols and Hunt [7] report a "marked deficit" as demonstrated by the Knox cube test in a 45 year old man, whose score was no better than the average 7 or 8 year old child's. For a former college student with a good record and a present Otis intelligence quotient of 120, this sounds indeed like a low score. But it happens that Weisenburg and McBride [22] have provided norms obtained with adults. The patient's score is not below the adult range, but near the lower quartile; and since the discrepancy between the data for adults and those obtained with school children suggests a pronounced loss of the ability with age, the patient's score may be relatively still higher when his age is taken into account. Another instance: Brickner [23] refers to his adult patient, who had a Stanford-Binet mental age of 12 years and 9 months, as making the score of a child. The Army data of 1917 and the later study by Weisenburg, Roe and McBride [24] show that such an interpretation, which is based on Terman's data obtained from school children, is quite wrong; the mean adult score on the 1916 revision appears to be between 13 and 14 years, and the score for Brickner's patient is lower than the mean by less than one-half the standard deviation (Weisenburg, Roe and McBride,[24] pages 9 and 59).

The failure to obtain normal control data of any kind, as in Goldstein's work, or the dependence on age norms for school children seems often to be based on the silent assumption that one knows how the "normal" adult will deal with the test problem or that a given test is so simple that any normal adult would succeed with it. No assumption could be more dangerous. One's ideas of the average intelligence are colored by one's occupation, cultural background and familiarity with the abstract and academic.

The divergence between what might be expected and what actually is done by normal persons can best be illustrated by data obtained from a test which has not been published. The test material consisted of shapes cut out of cardboard and five identical wooden triangles with which the cardboard patterns were to be reproduced, two or more being used for each pattern. In the figure, several of the test patterns and some of the solutions are represented. The significant fact is that no pattern could be devised which was so easy that all patients in the public wards of a general hospital would succeed with it in one minute, even though other tests showed that one was not dealing with a population of mentally deficient persons. Some of the failures were almost incredible. An extremely intelligent technician, who was a college graduate and a biochemist, was unable to reproduce pattern *a* in the figure in two minutes, although she recognized that only two blocks were to be used and although with more practice on the test she proved able to solve difficult problems, beyond the range of most persons. A number of patterns, such as *b*, were tried and proved persistently difficult to a quarter or less of the normal population. Even pattern *c* was difficult; in both *b* and *c* many subjects apparently could not keep the orientation of the two blocks distinct. Although they knew that the task was to reproduce the pattern exactly, they would make pattern *d*, perhaps, for pattern *c*, or even pattern *f* for pattern *e*. Such persons often could not see just where the trouble was when they were told that the solution was not satisfactory. Finally, such solutions as making pattern *h* for pattern *g* were observed not once but a number of times; the subject would finish the arrangement of blocks and, incredibly, ask whether it was right.




Test problems and representative failures made by normal subjects. Diagrams *a*, *b*, *c*, *e* and *g* represent patterns cut out of cardboard and placed before the subject, who was to reproduce the pattern with wooden blocks in one minute. Broken lines inserted in diagrams *a*, *b* and *g* show how the blocks were placed in a correct solution, but these lines were not given in the test patterns. The subject was given five identical wooden triangles (with 30, 60 and 90 degree angles) and was told to use as many as he needed to make an exact copy of the cardboard pattern. The hatched diagrams represent solutions of a kind made by a fifth or more of the normal population: *d* is an attempted copy of pattern *c*; *f*, a copy of pattern *e*, and *h*, a poor attempt to copy pattern *g*.

These are of course extreme examples, but they illustrate a kind of ineptitude in solving abstract problems that is to be observed in less degree with a number of tests and among persons who have no defect of economic and social adjustment and whose Binet score may be within normal limits. If the described behavior were an

22. Weisenburg, T., and McBride, K. E.: Aphasia: A Clinical and Psychological Study, New York, Commonwealth Fund, 1935.

23. Brickner, R. M.: An Interpretation of Frontal Lobe Function Based upon the Study of a Case of Partial Bilateral Frontal Lobectomy, Research Nerv. & Ment. Dis., Proc. **13**:259-351, 1934.

24. Weisenburg, T.; Roe, A., and McBride, K. E.: Adult Intelligence: A Psychological Study of Test Performances, New York, Commonwealth Fund, 1936.

isolated instance, it could be dismissed; but it was observed repeatedly with this test. No one, I think, will find it credible; and this means that if one found such behavior in a case of cerebral damage, and had no test data from unsophisticated adults, one would be bound to conclude that the behavior was determined by the presence of the lesion. There is an obvious similarity of the test to some of Goldstein's (Bolles and Goldstein [25]), for which no normal control data are provided.

In subsequent work, with the object of getting improved test instruments for the unsophisticated adult, I have tested approximately 300 patients in the public wards. Instead of composite tests, separately standardized ones were used, some of which were especially designed to avoid literary and academic sophistication. If by "intelligent" one means making an average score in a number of intelligence tests, then it may be said that an intelligent person with no suspicion of cerebral injury or disease may do very badly, or may give apparently very stupid answers, in a single kind of test or on individual test items. Such test material tends to be eliminated in the standard composite tests by the ordinary routine of item selection, but in special tests which have not been standardized there is a real danger of assuming that a variation from the norm which is frequently obtained for the normal population can be due only to the effects of cerebral injury. It need hardly be added that such variability is less likely to appear in an academic population and that neither school children nor college students make an adequate control group for older subjects or for persons not engaged in clerical work.

The work of Weisenburg and McBride [22] and of Weisenburg, Roe and McBride [24] with normal subjects seems strangely unheeded. For any one who is proposing to set up a test battery for clinical analysis of cerebral function, these authors have provided the groundwork of normal control data. Dr. Morton and I have also attempted to supplement their test battery (Hebb,[26] Hebb and Morton [27]) and to give a greater variety of tests in which roughly satisfactory adult norms are provided.

25. Bolles, M., and Goldstein, K.: A Study of the Impairment of "Abstract Behavior" in Schizophrenic Patients, Psychiatric Quart. **12**:42-65, 1938.

26. Hebb, D. O.: Verbal Test Material Independent of Special Vocabulary Difficulty, J. Educ. Psychol. **33**: 691-696, 1942; Footnote 26.

27. Hebb, D. O., and Morton, N. W.: The McGill Adult Comprehension Examination: "Verbal Situation" and "Picture Anomaly" Series, J. Educ. Psychol. **34**: 16-25, 1943.

## REVIEW OF CASE REPORTS

### UNILATERAL "LOBECTOMY"

There are thus two hurdles for investigators who would attempt to show that defects result from simple loss of frontal lobe tissue. One is to determine the size and locus of the surgical lesion and to verify the absence of significant pathologic changes which complicate the picture. The second is to obtain normal control data. Criticism on both scores is relevant to much published work. In the following review, published reports of removal of the frontal lobe are evaluated with respect to the adequacy of such anatomic and behavioral controls.

*Negative Conclusions.*—The difficulty with anatomic and pathologic controls is in general less for the investigator who attempts to show that a given defect does not follow frontal lobectomy. It has already been pointed out that the minimal extent of a lesion is usually easier to determine than the possible maximal extent. The anatomic data of Jefferson [16] and Lidz,[28] who concluded that no defects follow unilateral lobectomy, might be suspect, however, for in removal of a tumor the destruction of normal tissue may seem to go farther back than it actually does. However, the reverse is true of atrophy and scar formation, and the results reported by Hebb [29] in 5 cases of removal of scars confirm the conclusions of Jefferson and Lidz.

None of these studies, including my own, utilized good normal control data but depended either on high postoperative scores or on comparisons of preoperative and postoperative scores in concluding that loss of frontal association areas has no detectable effect on test scores. Emphasis here is on the word "detectable"; a better conclusion would be that no defect has been demonstrated. For comparison of preoperative and postoperative scores is not valid except to show that a surgical removal from the frontal lobe leaves intelligence as high as, or higher than, that with a pathologic lesion. Obviously a high preoperative score might have been still higher if the cerebral tumor or scar had not occurred in the first place. From these papers, and from that of Stookey, Scarff and Teitelbaum,[18] several conclusions are justified: (1) A high level of functioning is possible after unilateral frontal lobectomy; (2) no clinically evident defects need follow, and (3)

28. Lidz, T.: A Study of the Effect of Right Frontal Lobectomy on Intelligence and Temperament, J. Neurol. & Psychiat. **2**:211-222, 1939.

29. Footnotes 11 and 17.

tests fail to demonstrate any loss of intellectual ability after the unilateral surgical removal of frontal lobe tissue when pathologic complications are minimized.

*Attempts at Localization (Positive Conclusions).*—Of the various attempts to show that surgical lesions of the frontal association areas produce definable defects, Rylander's [30] study is unique in actually using a carefully chosen normal control group. As a result, it provides important and extremely interesting psychologic information concerning the sequelae of removal of tumors of the frontal lobe. His study would have been beyond criticism if he had concluded only that the defects, some of them so slight as to be demonstrable only by group comparisons and not in the individual patient, were those that characterize the postoperative course after removal of tumor. It is an undoubted fact that the removal of a large tumor is likely to leave the patient with more or less pronounced mental changes, and Rylander's excellent method adds definite information about their nature. But he went further and reached the conclusion that the defects which he described were due to the surgical excision of frontal lobe tissue. No such conclusion is justified. As has already been seen, the removal of a tumor may not leave the rest of the brain in a normal condition. Further, in his 32 cases Rylander included 1 case in which the anterior cerebral artery was believed to have been clamped at operation, cases in which a tumor could not be completely removed and cases in which the tumor was of a type which could be expected to recur. Here, the described mental and moral defects may be due to the surgical removal, to the added pathologic destruction or to both; but they cannot be put down simply to the uncomplicated loss of frontal lobe tissue.

In another study on a large group, Halstead [31] encountered this difficulty, as well as the problem of getting normal control subjects. Halstead's data present no evidence that his cases were any more suitable than are most cases of tumor for the localization of frontal lobe function; the inclusion of cases of incomplete removal of tumor, of glioblastoma (a rapidly recurrent type of neoplasm) and of hemiparesis or aphasia not accounted for by the extent of the surgical lesion means that the patients had serious pathologic as well as surgical lesions; and defects cannot be unambiguously ascribed to the surgical removals. The inclusion of cases of aphasia with the cases of lesions of the frontal pole further complicates interpretation of the group scores.

As to the control group, Halstead gave no data except to state that the ages of his 11 normal subjects ranged from 12 to 56 years. The patients with lesions of the frontal lobe, on the other hand, were all adults, from 31 to 63 years of age. The actual distribution of ages of the normal subjects is not known, and any information about their occupations and degree of education is lacking. Since the clinical subjects included an unskilled laborer, a farmer and a truck driver, one cannot be sure that the comparison of normal subjects and patients with lesions of the frontal lobe is valid with respect either to age or to sophistication.[32] More data are necessary before one can be sure that the quantitative defects are characteristic even for patients with removal of the frontal lobe with pathologic complications.

Other reported cases need not be examined in so much detail. German and Fox,[33] Penfield and Evans [9] and Ackerly [34] described defects clinically evaluated and did not depend for their positive conclusions on test methods. In no case is there reason to be sure that the pathologic conditions were suitable for the localization of function, although, as in Rylander's monograph, data of considerable psychologic significance are given.

### BILATERAL "LOBECTOMY"

There have been a number of cases of bilateral removal of the frontal association areas. From this number can be excluded such cases as Ackerly's, in which the surgical destruction was unilateral and the second lobe was pathologically

30. Rylander, G.: Personality Changes After Operations on the Frontal Lobes: A Clinical Study of Thirty-Two Cases, London, Humphrey Milford, 1939.

31. Halstead, W. C.: Preliminary Analysis of Grouping Behavior in Patients with Cerebral Injury by the Method of Equivalent and Non-Equivalent Stimuli, Am. J. Psychiat. **96**:1263-1291, 1940.

32. Age differences also invalidate the comparison of patients with lesions of the frontal lobe and other patients. The average age of the group with lesions of the frontal lobe was 44.2 years (range, 31 to 63 years); the average age for the other patients, 27.7 years (range 15 to 35 years, with 1 patient 51 years of age). The difficulty is even greater with the data of Halstead and Settlage (*Arch. Neurol. & Psychiat.* **49**:489-506 [April] 1943), in which 3 patients aged 31 to 51 years with lesions of the frontal lobe are compared with 3 patients 19 to 25 years old with lesions of other parts of the brain. The type of behavior studied is affected by age; we do not know, therefore, whether the lower scores for patients with lesions of the frontal lobe are due to the locus of the lesion or to age.

33. German, W. J., and Fox, J. C.: Observations Following Unilateral Lobectomies, Research Nerv. & Ment. Dis., Proc. **13**:378-434, 1934.

34. Ackerly, S.: Instinctive, Emotional and Mental Changes Following Prefrontal Lobe Extirpation, Am. J. Psychiat. **92**:717-728, 1935.

involved, with no surgical attempt to remove an area of possible dysfunction. As has been seen, in such cases positive localization of function is no more possible than if there had been no surgical intervention at all.

The first case of bilateral surgical removal described is that of Brickner,[35] who arrived at the conclusion that his patient had "a single, basic intellectual deficit," which he called a loss of synthesis. There are theoretic difficulties about this concept which will be discussed in a later section. Clinically, there were serious social abnormalities in this case, and Brickner and many subsequent writers have attributed these defects to a simple loss of tissue. There is no sufficient basis for the conclusion. First is the known fact, already stressed, that large tumors tend to be accompanied by pathologic changes in the rest of the brain. The surgeon's report at operation confirms the probability of widespread damage and makes it clear that little was known of the status of the remaining brain tissue after operation. Veins were observed to be thrombosed before the operation began, and it is not stated that the preoperative thrombosis was only in the tissue removed. Much of the field of operation could not be seen by the surgeon at all. Although the line of section was far back, one anterior cerebral artery was not seen, nor apparently the other; so either artery may have been thrombosed or shut off at operation. The deeper parts of the tumor were dissected out with a finger, without visual guidance. Necrotic tissue could hardly have been cleaned up, so that scar formation may have resulted; and the postoperative course of repeated epileptic fits is confirmatory. Further, the patient's postoperative deterioration appears to have fluctuated rather greatly. If so, the cause could not have been a static loss of tissue but is likely to have been related to the epilepsy. Electroencephalographic studies show clearly that epileptoid dysfunction can occur distinct from actual convulsions. Mental slowing without any obvious objective sign of an attack has also been described (Hunt, Wittson and Harris [36]; Hebb and Penfield,[1] page 431). In his latest report on the case of bilateral "lobectomy," Brickner [35a] has described increased irritability for a full day preceding an epileptic attack, a symptom which suggests strongly that it, and other fluctuations of social adaptation, arose from epileptoid states, even when an actual convulsion did not follow. The case is that of a deteriorated epileptic patient with a large removal of the frontal lobes but, also, with an unknown degree of pathologic destruction in the rest of the brain. In such a case there is no evidence whatever as to the effect of a similar removal of frontal lobe tissue without pathologic complications.

Another extensive study of a case of bilateral removal of a tumor was reported by Nichols and Hunt.[7] Like Brickner's, their patient was undoubtedly deteriorated. However, their attempt to define the nature of the loss more exactly by the use of tests cannot be considered successful, for their patient was 45 years old and they drew their control data from college students and from children's mental age norms. Their interpretation of results with the Knox cube test has already been referred to. A mental age score of 7 years sounds like a definite loss for a formerly intelligent adult, but it is actually well within the range of adult scores (Weisenburg and McBride [22]) and cannot be evaluated at all before one has norms not merely for adults but for adults in the later decades of life.

In this case, too, there are grave difficulties concerned with the pathologic data. Tumor tissue was left in the middle fossa, and in the report no consideration is given to the lasting effects of pressure before operation. Freeman and Watts [2] (page 68) have quoted Nichols as saying that the presence of air in the region of the chiasm, in a postoperative pneumoencephalogram, showed that no pressure from the tumor remained in this region. What this report neglects is the effect of earlier pressure in the supraoptic or the hypothalamic region, in which atrophy might have occurred. In the encephalogram published by Nichols and Hunt there was evidence of pronounced atrophy and regrowth of tumor tissue.[37] Social and intellectual defects can as well be related to these pathologic conditions as to the surgical excision. Like Brickner's case, the case of Nichols and Hunt shows clearly that lasting deterioration may follow the removal of a large and compressing tumor from the frontal region; it gives no good evidence as to the effect of extirpating frontal association areas in more favorable circumstances.

In the case described by Mixter, Tillotson and Wies,[8] an apparently conservative extirpation of atrophied tissue from both frontal lobes was followed by notable improvement and later relapse. The conclusions drawn by the authors were negative; that is, they did not ascribe symp-

35. Brickner, R. M.: (*a*) Bilateral Frontal Lobectomy: Follow-Up Report of a Case, Arch. Neurol. & Psychiat. **41**:580-585 (March) 1939; (*b*) Footnote 23; (*c*) Footnote 6.

36. Hunt, W. A.; Wittson, C. L., and Harris, H. I.: Temporary Mental Impairment Following a Petit Mal Attack, J. Abnorm. & Social Psychol. **37**:566, 1942.

37. In a personal communication, Dr. Nichols reports pronounced electrical abnormalities recorded from the residual tissue of both frontal lobes.

toms to the surgical removal. The fluctuation of symptoms, with recovery first and then relapse, shows at least that the defects which disappeared temporarily are to be ascribed to a variable physiologic condition and not to the permanent surgical removal. Gibbs, Gibbs and Lennox [38] reported improvement in the electrical record after operation in this case, and it seems quite possible that, as Freeman and Watts have suggested, a more radical removal might have had better results, particularly if it had been possible to keep postoperative scarring to a minimum.

Other cases may be referred to briefly. Karnosh [10] described a case in which operation was performed for tumor of a type which tended to recur, and Gantt [39] reported 2 cases, in 1 of which, however, there was atrophy or congenital absence of one frontal lobe instead of surgical removal. Both reports described serious deterioration, but there is no reason to believe that the pathologic situation was suitable for interpretation of the normal function of the frontal lobe.

With the exception of the cases reported by Hebb and Penfield and by Mixter, Tillotson and Wies, in both of which improvement is reported to have followed operation, all bilateral operations on the frontal lobe have been done for brain tumor, and in such cases the odds are strongly against the clearcut removal that is needed for the analysis of function. In the cases of tumor in which adequate data are provided there are positive indications of serious pathologic involvement. Even in the case reported by Mixter, Tillotson and Wies it must have been difficult to know how far posteriorly the region of atrophy extended, and the postoperative course indicates strongly that the remaining brain tissue was pathologically involved.

In contrast to these pathologic conditions is the clearcut line of section shown by postoperative pneumoencephalograms in Hebb and Penfield's case and the absence of any great amount of atrophy. There were still occasional abnormalities in the electroencephalogram, but in general the part of the brain which remained after operation was as undamaged as one could hope for in a clinical case. An exceptional lack of psychologic abnormality accompanied this exceptional absence of pathologic change. It is unlikely that the two facts are not related.

38. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Cerebral Dysrhythmias of Epilepsy: Measures for Their Control, Arch. Neurol. & Psychiat. **39**:298-314 (Feb.) 1938.

39. Gantt, W. H.: Impairment of the Function of Adaptability as Measured by a Simple Conditioned Reflex Test in Certain Psychogenic Contrasted with Organic Diseases, South. M. J. **31**:1219-1224, 1938.

## FREEMAN AND WATTS'S INTERPRETATION BASED ON FRONTAL LOBOTOMY

Freeman and Watts [2] have based an elaborate psychologic interpretation of function of the frontal lobe on the study of a series of 80 cases of "lobotomy," an operation in which most of the fibers connecting the frontal association areas with the rest of the brain are cut. Their theory of loss of foresight resulting from injury to the frontal lobe will be discussed in a later section. More important for the present is the authors' initial assumption that the temperamental changes in their patients are deficit phenomena.

Now the evident fact is that the operation they describe must produce fairly extensive pathologic changes. Once again one is dealing with a purely surgical procedure complicated by pathologic changes, without anything which permits one to eliminate the latter as a source of symptoms. Most significant, in this respect, are the instances of recovery with later relapse following the same form of operation which produced a number of lasting recoveries (Freeman and Watts,[2] page 81).

The question here is: What produced a transient recovery and yet permitted relapse? The cut fibers in the frontal lobes do not regenerate. Some recoveries must have been due to a reversible process, and therefore others may also. As in the similar course which is seen more often with shock therapy, there is suggested a correlation between recovery and a sometimes transient, but with lobotomy more often a chronic, physiologic disturbance. Electrical evidence and the clinical course after the excision of small areas near a sensory or motor region show clearly that surgical procedures are followed by a local cerebral disturbance which may have effects at some distance and which usually disappears slowly during a period of weeks or months. Freeman and Watts' observation (pages 206 to 207) that a characteristic frontal lobe syndrome appears after operation and then slowly disappears, leaving less exaggerated chronic symptoms, is further evidence that some symptoms referable to the frontal lobe are a product of physiologic disturbance. If lobotomy tends to leave extensive scar formation and vascular damage, the physiologic disturbance could become chronic, although diminished presumably from its higher level immediately after operation.

Intrinsically, this may be a less likely explanation of personality changes than that an essential tract is interrupted by lobotomy. Yet it is to be remembered that the abnormalities of personal adjustment in the cases reported by Freeman and Watts were highly variable and that, as will be

seen later, their attempt to reduce the disturbance to a single defect (of foresight with respect to the self) is neither psychologically acceptable nor in agreement with a number of their case histories. The variation from one case to another suggests, at least, a complication of the surgical incisions by various pathologic lesions. Further, the tactlessness and release of malice which the authors describe did not occur during the period of improvement in Hebb and Penfield's patient, or apparently either in the patient whose case is reported by Nichols and Hunt or in the one described by Mixter. Tillotson and Wies. If the defects described by Freeman and Watts are deficit phenomena, and are not due to cerebral dysfunction, they should occur with lobectomy as well as with lobotomy.

There have been a good many other references in the literature to lobotomy, a discussion of which is not within the scope of this paper. The criticisms that apply to the attempt by Freeman and Watts to analyze normal functions of the frontal lobe on the basis of the clinical phenomena of lobotomy apply also to similar attempts by other authors. Prefrontal lobotomy is a landmark in psychiatric therapy but has yet to provide any interpretable evidence concerning what goes on in the normal frontal lobes.

## THEORETIC INTERPRETATIONS OF FUNCTION OF THE FRONTAL LOBES

In a number of instances authors have tried by a single concept to explain the defects observed in cases of operation on the frontal lobes, and thus to achieve a theoretic statement of the functions of the frontal association areas. In discussing three of the most important formulations one may show at least the difficulties to be encountered in such an attempt.

Brickner [23] has tried to show that his patient with the bilateral operation on the frontal lobes had "a single, basic intellectual deficit," referred to as a loss of the power synthesis of "simpler thought processes" into "more complex structures." Freeman and Watts have devised a somewhat more elaborate theory, to the effect that the frontal lobes are concerned with foresight while the rest of the brain mediates intelligence and memory of the past. The foresight associated with the frontal lobes is particularly with respect to personal acts and "the relation of the self to the self" (Freeman and Watts,[2] page 298). Goldstein and Katz [3] ascribed all defects referable to the frontal lobe to a "loss of abstract behavior." Differing as these three concepts do, they have one thing in common when they are applied to the explanation of the clinical phenomena. They explain at once too much and too little. They are too broad and ill defined to be meaningful, and they are too likely to lead to an *ad hoc* interpretation of symptoms. The attractiveness or plausibility of such formulations is part of their danger; it is too easy to think of all the facts they account for and not to ask whether there are others which they do not explain or whether symptoms are absent which they require.

In Brickner's case there were certainly defects of learning and memory, or of association, and a good argument is made for regarding other things, too, as a loss of "synthesis." Yet there are many defects which the patient did not have and which might have been expected to be apparent psychologically from the same loss. The concept will not advance scientific knowledge until it is made less inclusive and its implications more specific, so that it can be tested empirically.

Freeman and Watts' theory of foresight with respect to the self seems actually not to arise from a satisfactory generalization of their data but to be based on the remark of 1 patient (Freeman and Watts,[2] page 120). The lack of foresight after lobotomy is supposed to be seen in tactless remarks and inappropriate acts; but apparently many of their patients had no regrets about such things after they were done, though regret would be implied if the tactlessness occurs only because the effect of a remark is not foreseen in advance. The authors' stress on the freedom from self consciousness that follows lobotomy suggests that many patients were no more concerned about inappropriate acts in the past than in the future. Finally, the frequent freedom from remorse and feelings of guilt after lobotomy seems to have no relation at all to the postulated functions of the frontal lobe, and in general one can say that the variety of postoperative changes described is greater than one would be led to expect from a lack of "foresight with respect to the self."

Goldstein's concept of "loss of the abstract attitude," or of "abstract behavior," is also open to the objection that it includes too much and too little. Behavior that seems to involve abstraction is called concrete and vice versa. Take as an example the copying of a V made with small wooden sticks. The patient makes instead an inverted V, which he says represents the eaves of a house. This is called concrete behavior. But to see an inverted V as a housetop involves abstraction, and it would surely be more concrete to respond to the configuration of the actual objects in front of the patient. What is really described seems to be a shift from one kind of abstraction to another. The fact that not only

signs of damage to the frontal lobe (Goldstein [40]) but amnesic aphasia (Goldstein [41]) and schizophrenia (Bolles and Goldstein [25]) can be reduced to a "loss of the abstract attitude" illustrates well the vagueness and inclusiveness of the term, which can have no value until one knows more precisely what defects are not included. One cannot very well treat three quite different deteriorations as due to a single basic deficiency without accounting for differences, as well as similarities.

In defending his theoretic conceptions, Goldstein [40] thoroughly confused the issues with which the present paper deals. For clarity, his criticism, particularly of Hebb and Penfield,[1] must be considered in detail.

To begin with, his discussion contains errors of fact. 1. He [40] (page 201) assumed that there were no preoperative defects in K. M., the patient who lacked both frontal poles, and stated that his theory would have to be reconsidered if there had been characteristic defects. Dr. Penfield and I thought we had stressed the preoperative defects: Certainly the patient lacked initiative, foresight and ability to handle new tasks, which Goldstein has listed as characteristic clinical signs of destruction in the frontal lobes. 2. Goldstein [40] has stated (page 192) that my failure to find psychologic shortcomings after unilateral operation on the frontal lobe (Hebb [17]) can be dismissed because I did not use the right tests for finding them. But the Arthur performance scale includes the Kohs block design and feature profile tests, used by Bolles and Goldstein [25] as a test of the abstract attitude; and the Stanford-Binet diagrams to be copied from memory are not different from Goldstein's except that they are much more difficult. The patients, including K. M., with bilateral damage did well on these tests. Moreover, K. M. was given a sorting test, the importance of which Goldstein has stressed, and spontaneously sorted objects according to (*a*) use, (*b*) size and (*c*) material (metal, paper, wood, glass): a total of three principles of classification, while the average for normal persons is two and three-tenths (Rylander [30]—the only available norm). 3. Goldstein speaks of K. M. as "admittedly not normal." What Dr. Penfield and I admitted was that the most rigorous search had discovered no defects in the patient, though we knew that this did not prove he had none. It is worth noting that Nichols and Hunt, also, using Goldstein's tests, failed to find loss of the abstract attitude in their patient with bilateral damage to the frontal lobes.

One must object on logical grounds to Goldstein's [40] emphasis on cases which support his interpretations and his disregard of those which are opposed (pages 189 to 192) and to his statement that negative findings "cannot ask for great consideration if the characteristic changes have been found in many other cases." The argument must be completely reversed. As I have tried to show in discussing the difficulties of getting satisfactory anatomic and pathologic data, it is the cases with fewest symptoms to which attention must be paid, since they are the ones in which the effect of pathologic complications is likely to be least. The "many other cases" to which Goldstein refers are the very ones which have been shown in this review to involve pathologic as well as surgical lesions, while the negative cases which Goldstein rejects are the ones in which operation was done to remove pathologically affected tissue.

Finally, one may consider Goldstein's interpretations of the improvement in K. M. following extirpation of both frontal poles. Goldstein argues, in brief, that the brain which lacks all the frontal association areas may function at a higher level than a brain in which less of this area is removed. The interpretation has some support in observations on other types of defect. A habitual mode of response may be persisted in as long as it is at all possible, although a new mode of response would be more efficient if a complete loss of the old mechanism forced the new adjustment. A patient may continue to use a crippled organ rather than shift to a previously unused one, and make the shift only when use of the injured organ is precluded. Instances cited by Goldstein [42] include the persistent attempt to use a partly paralyzed right hand in writing although the left would be more effective, and the formation of a pseudofovea in cases of complete hemianopsia but not in cases of hemiamblyopia.

In these instances, however, the substitute functions are recognizably different from the original, either in mode of performance or in end result, whereas in the case of K. M. it is impossible to distinguish his intellectual functioning from that of normal persons. There is no evidence that the loss of frontal lobe tissue affects his behavior in any way. To argue, therefore, that a large bilateral removal leads to a higher level of intellectual performance than a smaller loss of tissue (apart from an explanation based on cellular dysfunction) makes two assumptions for which

40. Goldstein, K.: The Mental Changes Due to Frontal Lobe Damage, J. Psychol. **17**:187-208, 1944.

41. Goldstein, K.: The Problem of the Meaning of Words Based upon Observation of Aphasic Patients, J. Psychol. **2**:301-316, 1936.

42. Goldstein, K.: The Organism, New York, American Book Company, 1939.

factual support is lacking: (1) that the intellectual defect which Goldstein regards as characteristic of injury to the frontal lobe are deficit phenomena and (2) that intellectual performance after cleancut "lobectomy" is qualitatively different from the normal. Also, this interpretation of K. M.'s improvement following operation totally disregards definite physiologic and clinical facts, namely, the change in the electroencephalogram, and the disappearance of frequent epileptoid states. These facts alone adequately account for the improvement.

## CONCLUSIONS

This paper stresses the failure to find psychologic defects that can be attributed to clean surgical injury of the frontal lobes. To avoid misunderstanding, let it stand as a first conclusion that operations on the frontal lobe are followed by defects in almost all cases. But a second conclusion must be that in almost all cases there are also pathologic changes, sometimes extensive, to complicate the surgical removal. The question that this paper has raised is whether the behavioral defects following operation are the result of the surgical removal or whether they are due to the presence of pathologic changes in the remaining part of the brain.

The evidence on which intellectual and moral defects have been attributed to the surgical removal of frontal lobe tissue is very poor. It has been obtained from (1) individual cases, in which the complication of the surgical lesion by extensive pathologic processes is at least highly probable, and (2) average scores for a number of cases indiscriminately grouped. The averages are affected by the inclusion of demonstrably unsuitable cases, and there is no reason to think that the defects are characteristic of all cases in the group. In the interpretation of scores, both for individual cases and for groups, there has been a repeated misuse of normal control data. The objection to ascribing psychologic changes to a surgical procedure alone, when there are also pathologic processes present, applies in cases of lobotomy as well as lobectomy; and there is evidence in the postoperative course after lobotomy to substantiate the objection. Finally, as I have tried to show, there is no possibility at all of interpreting normal functions on the basis of pathologic cases in which surgical treatment is not attempted.

Sweeping as the conclusion is, therefore, it can only be said that no one as yet has produced convincing support for any of the varied ascriptions of normal function to the frontal association areas of the human brain. No one has proved that any single form of normal behavior is dependent on this part of the brain or that a clean surgical removal of both frontal poles has any effect on behavior.

These statements may be taken as meaning more than they do and must be qualified on two points. In the first place, I do not disparage the value of a number of careful studies as analyses of dysfunction or abnormal behavior, although these studies may not contribute to the specific question of the localization of function. In the reports of Ackerly, Brickner, Goldstein, Nichols and Hunt and Penfield and Evans, and particularly in the monographs of Freeman and Watts and of Rylander, there are analyses of behavior which no student of abnormal psychology can disregard. These studies are informative, just as the study of psychosis is informative. Furthermore, when enough is known of cerebral functioning to permit a physiologic interpretation, the observations in question will assume even more significance.

To qualify my conclusions further, I must emphasize that I do not mean that the frontal lobes have no intellectual or moral function. It must be assumed that the region has an important role in behavior, and there are many possibilities which cannot be ruled out. Failure to prove that it has certain functions does not show that it has none, and there is not the remotest basis for saying that the frontal lobes have, for example, no intellectual functions (as some authors have done). From the postoperative behavior of K. M., one may say that the frontal poles of the brain are not necessary to a good day by day adjustment in society or to a good performance on intelligence tests; but this is a limited statement, especially since cerebral injuries affect the correlation of intelligence test scores and behavior in other situations (Hebb [43]). It is still possible that long term planning and initiative (Penfield and Evans [9]), creative work and capacity for radical readjustment may be notably impaired by lesions of the frontal lobe.

The determination to find defects in performance of laboratory tests after injury to the frontal lobe and the lack of attention to high scores (which actually are reported by most investigators who have used intelligence tests) misses a most important problem. Why is there so little direct evidence of intellectual defect from cerebral damage in any area other than that of speech? I have tried elsewhere to summarize the evidence concerning the intellectual effects

43. Hebb, D. O.: Intelligence in Man After Large Removals of Cerebral Tissue: Defects Following Right Temporal Lobectomy, J. Gen Psychol. **21**:437-446, 1939.

of damage to the mature brain. The mean reported intelligence quotient following cortical extirpations, for example, is 108, a score much higher than the normal for adults (Hebb [44]). In discussing such facts, an explanation was sought in an apparent difference of effect between early and late injury to the brain. Apparently, injury in infancy has a much greater effect on later test scores than one which occurs at maturity. This suggests that extirpation of frontal lobe tissue in the infant would have a greater effect than it has in the adult, and hence that the frontal lobes may be more important in development than in later life. However, this is not true of the frontal lobes alone but can be applied with equal validity to other parts of the cerebral cortex except the speech areas; so an essential problem remains. Even if the hypothesis concerning the difference in effect between early and late injuries proves to be acceptable, there is still the question of the way in which the nonspeech areas of the cortex cooperate with the speech areas in normal intellectual function, and it is unlikely that the special question of the adult role of the frontal association areas will be solved apart from this more general problem.

*Therapy.*—For the physician or surgeon the chief interest of this study is in its showing that a large bilateral removal of frontal lobe tissue is not inconsistent with an excellent clinical recovery, and in establishing the probability that signs referable to the frontal lobe and behavioral defects following most operations on this region are due to complicating pathologic events, not to the surgical removal.

It is important to stress, also, that behavioral deterioration appears to be more severe or more frequent after operation for large tumors than after other extirpations. The single case of Rylander's in which there seemed to be no deterioration was one of operation for abscess. In Halstead's series, of 26 cases, the highest and fourth highest scores on the "per cent of objects grouped" were made in the 2 cases in which a scar had been removed. In the various reports of bilateral frontal lobectomy, the 2 patients whose operations were for the removal of scars were the only ones who could be freed from detention (Mixter, Tillotson and Wies,[8] Hebb and Penfield [1]). One of the 2 patients had a relapse, but the removal of scar tissue in his case was conservative. Cases of removal of scar tissue include also the extraordinary record of M. M. (Hebb [17]), with an intelligence quotient higher than 152 after amputation of the left frontal pole.

Consequently, radical treatment of a traumatic condition or scar may leave the patient in better condition than might be expected by the surgeon who is more familiar with the sequelae of operations for tumor. A further suggestion implicit in the evidence is that thorough cleaning up of tissue which is necrotic or not well vascularized is important not only for the avoidance of definitive epilepsy (Penfield [19]) but for the general mental status of the patient.

## SUMMARY

A patient with bilateral frontal extirpation was observed to have made a good social and economic adjustment six years after operation.

It is concluded that though this patient may show some defect in planning for the distant future, the defect is not clearly demonstrated or shown to be due to the cerebral destruction. There is no defect of foresight for the immediate future as shown by tactless remarks or inappropriate social behavior.

An analysis of methodologic difficulties in getting adequate anatomic, pathologic and normal control data suggests that these problems have not been sufficiently appreciated and have led to error in the interpretation of symptoms referable to the frontal lobes.

A review of published case reports of removal of the frontal lobe indicates that no one has as yet shown that defects follow a simple loss of tissue from man's frontal lobes; the loss must, presumably, have some effect, but it is hard to demonstrate and its nature is not yet clear.

The implications of the evidence for surgical treatment, particularly of traumatic injury, are that social and intellectual defects need not follow an uncomplicated bilateral excision of tissue from the anterior part of the frontal lobes.

Yerkes Laboratories of Primate Biology, Inc.

44. Hebb, D. O.: The Effect of Early and Late Brain Injury upon Test Scores, and the Nature of Normal Adult Intelligence, Proc. Am. Philos. Soc. **85**:275-292, 1942.

# POLYCYTHEMIA AS A NEUROSURGICAL PROBLEM

## A REVIEW, WITH REPORTS OF TWO CASES

JOHN H. DREW, M.D., AND FRANCIS C. GRANT, M.D.
PHILADELPHIA

That polycythemia should present a problem to the neurosurgeon will seem, to many, a novel idea. However, recognition of the remarkably high incidence of complications of the central nervous system associated with polycythemia will show that the possibilities are not so remote as they at first appear. In the fields of general medicine and surgery, differential diagnoses are many, as related both to similar and to dissimilar processes. In neurosurgery, not only is the field itself relatively narrow, but the actual number of differential problems is fewer. The immediate chief concern in cases of intracranial disease is whether or not the patient has an operable condition. The lesions commonly associated with this aspect of the problem include intracranial neoplasms, hemorrhage, abscess, infections, hypertensive cardiovascular disease, degenerative lesions and diseases of the eye producing papilledema. Less common are such conditions as pseudotumor,[1] renal disease with uremia[2] and blood dyscrasias.[3] Polycythemia is a member of the last group. It is the part played by this condition as a differential and operative problem to which we wish to call attention in the following case reports and discussion.

The extreme frequency of lesions of the central nervous system in cases of polycythemia has long been recognized.[4] Of 62 patients with this condition at the Hospital of the University of Pennsylvania in the last fourteen years, marked changes of this nature, ranging from facial weakness to complete hemiparesis or stupor, have been present in 13. All these patients were admitted to the medical wards and were studied as cases of polycythemia, and in no instance was the neurosurgical service asked to see a patient because a tumor of the brain was suspected. The explanation of this lies in the following statement: " . . . the association of polycythemia rubra vera with intracranial neoplasia is an event of the greatest rarity," [5] and in the fact that all of these cases were recognized and verified instances of polycythemia.

### IS POLYCYTHEMIA RELATED TO LESIONS OF THE CENTRAL NERVOUS SYSTEM?

Attention has been called by many writers[6] to the possible occurrence of polycythemia as the direct result of lesions of the central nervous system. In 1927, the disease was produced

From the Department of Neurosurgery, Hospital of the University of Pennsylvania, and the Harrison Department of Surgical Research, University of Pennsylvania Schools of Medicine.

1. Stough, J. T.: Choking of the Optic Discs in Diseases Other than Tumor of the Brain, Arch. Ophth. **8**:821-830 (Dec.) 1932.

2. Cushing, H., and Bardley, J.: Subtemporal Decompression in a Case of Chronic Nephritis with Uremia, with Especial Consideration of the Neuroretinal Lesion, Am. J. M. Sc. **136**:484-504, 1908.

3. Mills, E. S.: Papilledema in Pernicious Anemia, Canad. M. A. J. **32**:546-548 (May) 1935. Schinck: A Case of Choked Disc with Thrombopenia, Ztschr. f. Augenh. **49**:265-280, 1923. Watkins, C. H.; Wagener, H. P., and Brown, R. W.: Cerebral Symptoms Accompanied by Choked Disc in Types of Blood Dyscrasia, Am. J. Ophth. **24**:1374-1383 (Dec.) 1941.

4. (*a*) Adams, L. J.: Polycythemia Vera with Special Reference to Nervous Manifestations: An Analysis of Nine Cases, Canad. M. A. J. **32**:128-132 (Feb.) 1935. (*b*) Brockbank, T. W.: Neurologic Aspects of Polycythemia Vera, Am. J. M. Sc. **178**:209-215 (Aug.) 1929. (*c*) Christian, H. A.: The Nervous Symptoms of Polycythemia Vera, ibid. **154**:547-554 (Oct.) 1917. (*d*) Fucher, T. B.: The Clinical Aspects of Erythremia, Boston M. & S. J. **191**:304-311 (Aug. 14) 1924. (*e*) Horder, T.: Remarks upon Vaquez' Disease with Special Reference to Complications and with Notes of Seven Cases, St. Barth. Hosp. Rep. **59**:153-167, 1926. (*f*) Lucas, W. S.: Erythremia or Polycythemia with Chronic Cyanosis or Splenomegaly, Arch. Int. Med. **10**:597-667 (Dec.) 1912. (*g*) Sloan, L. H.: Polycythemia Rubra Vera: Neurologic Complications, Arch. Neurol. & Psychiat. **30**:154-165 (July) 1933. (*h*) Tinney, W. S.; Hall, B. E., and Giffin, H. Z.: Central Nervous System Manifestations of Polycythemia Vera, Proc. Staff Meet., Mayo Clin. **18**:300-303 (Aug. 25) 1943. (*i*) Watson, J. H.: Polycythemia Vera (Vaquez's, Osler's Disease): A Description of a New Clinical Entity, with a Note on a Method of Estimating the Viscosity of the Blood, Liverpool Med.-Chir. J. **26**: 33-49, 1906.

5. Carpenter, G.; Schwartz, H., and Walker, A. E.: Neurogenic Polycythemia, Ann. Int. Med. **19**:470-481 (Sept.) 1943.

6. (*a*) Baserga, P.: Polycythemia from a Lesion of the Diencephalic Hypophysis, Policlinico (sez. med.) **41**:17-24 (Jan.) 1934. (*b*) Carpenter, Schwartz and Walker.[5] (*c*) Castex, M. R.: Erythrocytosis and Erythremias: Etiology, Physiology and Pathogenesis,

*(Footnote continued on next page)*

experimentally by Schulhof and Mathies[7] by the injection of siliceous earth into the diencephalic region of rabbits. By far the greater number of lesions observed clinically have been those associated with infections and degenerative lesions, such as encephalitis and Parkinson's disease, or pituitary syndromes of the Cushing type, with a miscellaneous scattering of other lesions. In all the cases reviewed by Carpenter, Schwartz and Walker,[5] with 3 exceptions, the diencephalic region was involved. These authors cited 2 cases of their own in which cerebellar hemangioblastoma was accompanied with polycythemia, which disappeared after operation and removal of the lesion.[7a] Their first patient showed mental confusion and weakness. There was bilateral papilledema of 3 D., and the cerebrospinal fluid pressure was 320 mm. of water. The red blood cell count was as high as 7,130,000; the hemoglobin content was 23 Gm. per hundred cubic centimeters. The lesion was found in the right cerebellar hemisphere. The second patient complained of headache. There was bilateral papilledema (marked); the cerebrospinal fluid pressure was 330 mm. of water. The red blood cell count reached 6,500,000; the hemoglobin measured 20 Gm. per hundred cubic centimeters. The lesion was in the left cerebellar hemisphere. In both cases the polycythemia subsided and had not recurred up to the time of the last follow-up observation—in the first case, thirteen months, and in the second case, eight months, after operation. That polycythemia might be the underlying pathologic condition was seriously considered in both these cases. However, the pronounced papilledema and the increased cerebrospinal fluid pressure seemed out of proportion to what might be expected to occur with polycythemia, and ventriculographic examination was done.

A brief review of the other 3 cases cited by these authors shows that Oppenheimer[8] mentioned a case of polycythemia in which a cerebellar medulloblastoma was found at autopsy—no details are given. Salus's[6g] patient had right-sided convulsions, with loss of consciousness and paresis of the right side. There were some acromegalic changes, as well as polyuria, glycosuria and impotence. The red blood cells numbered 6,900,000. Autopsy revealed a sarcoma of the convexity of the left frontal lobe. The patient whose case was described by Meiner[9] had epileptiform attacks, spastic hemiplegia of the left side and symptoms characteristic of involvement of the right frontal lobe. The heart and liver were enlarged. The cerebrospinal fluid pressure was 250 to 300 mm. of water, and there were prominent choked disks. The red blood cell count was as high as 8,500,000; the hemoglobin concentration was 135 per cent. Operation showed a diffuse glioblastoma multiforme of the right postcentral convolution and of the angular and supramarginal gyri. The patient received postoperative roentgen therapy, which resulted in the reduction of the red blood cell count to 5,500,000 and of the hemoblobin content to 85 per cent. Seven months thereafter the spleen became enlarged, and the patient died three months later with a normal blood picture.

To the 5 cases just reviewed, we wish to add 3 more from the literature and 1 of our own, in which a subdural hematoma, instead of a cerebral tumor, was found.

CASE 1.—E. S., a 63 year old white woman, was referred to the neurosurgical service of the Hospital of the University of Pennsylvania on July 21, 1944, with the chief complaint of numbness of the left side of the body and pain at the base of her skull.

The patient had apparently been fairly well until June 1, 1944, when she had a draining left ear. She gave a vague history of having hit the left frontal region of her head on a cupboard door in February, without loss of consciousness. In April 1944, she began to have dizzy spells, in which the room seemed to revolve around her from right to left. One of the attacks lasted two days. During that time she tended to fall to the right whenever she attempted to walk. She had no visual trouble at that time. She complained of a "hot feeling" in her head. On May 26, she noticed that her left foot felt numb and queer; and on May 23, when getting into the bathtub, she found that she could not tell heat or cold with her left foot. One month later, her left hand became numb. On June 1, she had a "thick sensation" in

Prensa méd. argent. **16**:693-713 (Oct. 30) 1929. (*d*) Da Rin, O., and Costa, D. L.: Influence of the Central Vegetative Nervous System on the Blood Picture, Clin. med. ital. **65**:303-345 (April) 1934. (*e*) Ferraro, A., and Sherwood, W. D.: Polycythemia in the Course of Neuropsychiatric Conditions, Psychiatric Quart. **11**: 19-33 (Jan.) 1937. (*f*) Guillain, G.; Lechelle, P., and Garcin, R.: Polyglobulia, With or Without Erythrosis, in Certain Hypophyseal-Tuberian Syndromes, Ann. de méd. **31**:100-114 (Jan.) 1932. (*g*) Salus, F.: Central Nervous Regulation of the Red Blood Picture, Deutsches Arch. f. klin. Med. **175**:214-220 (May) 1933.

7. Schulhof, K., and Mathies, M. M.: Polyglobulia Induced by Cerebral Lesions, J. A. M. A. **89**:2093-2094 (Dec. 17) 1927.

7a. Walker has since reported a third case of cerebellar hemangioblastoma associated with a polycythemia which disappeared after removal of the neoplasm (Walker, A. E.: Neurogenic Polycythemia: Report of a Case, Arch. Neurol. & Psychiat. **53**:251-253 [March] 1945).

8. Oppenheimer, B. S.: Vascular Occlusion in Polycythemia Vera, Tr. A. Am. Physicians **44**:338-344, 1929.

9. Meiner, E.: Brain Tumor Complicated by Polyglobulia, Schweiz. med. Wchnschr. **66**:338-339 (April 4) 1936.

her throat and some difficulty in swallowing. At the same time, her vision began to be blurred, and double vision developed. These changes became progressively worse up to the time of her admission. On admission, she was unable to read a newspaper and said she felt as though she were looking through a tunnel. Every time she attempted to sit up in bed she had a severe stabbing pain in the occipital region. There was no nausea, vomiting or generalized headache. She complained of tiring easily and of becoming dyspneic on long walks. Although her appetite had been good, she had lost about 20 pounds (9.1 Kg.) in the past seven months. She complained of chronic constipation. Her face, she thought, had been slightly redder than normal for the past two years. She had never had convulsions.

Physical examination revealed a slightly undernourished woman. She did not seem acutely ill and was fairly cooperative, but showed a tendency to become mentally confused. Her general coloring was a moderately dusky red. The mucous membrane of the mouth and pharynx was conspicuously injected. The chest was entirely normal. The heart was not grossly enlarged; there were no murmurs. The edge of the liver was palpable 4 fingerbreaths below the costal margin. The spleen was not palpable. There was no clubbing of the fingers or cyanosis of the nail beds. The superficial veins of the extremities were tortuous. The blood pressure was 160 systolic and 95 diastolic when she was in supine position. The Kolmer and Kline reactions of the blood were negative. Urinalysis revealed nothing significant. The hematologic findings before and after her admission to the University Hospital are given in table 1.

TABLE 1.—*Hematologic Findings in Case 1*

| Date | Red Cells (Cu. Mm.) | Hemoglobin, % | White Cells (Cu. Mm.) | Hematocrit Reading | Miscellaneous Data and Treatment |
|---|---|---|---|---|---|
| 6/ 1/44 | 7,350,000 | 144 | 8,200 | .. | 270,000 platelets |
| 6/ 6/44 | 6,910,000 | 129 | ..... | .. | 500 cc. of blood drawn 6/3 and 6/5 |
| 6/ 9/44 | 5,350,000 | 108.9 | 8,800 | .. | 500 cc. of blood drawn 6/7 |
| 7/10/44 | 6,820,000 | 120 | ..... | .. | |
| 7/22/44 | 6,900,000 | 120 | 9,400 | 72 | Patient admitted to University Hospital; ventriculogram 7/27 |
| 8/ 2/44 | ..... | 116 | 11,500 | 64 | 500 cc. of blood drawn 8/2 and 8/3 |
| 8/ 5/44 | ..... | 102 | 14,500 | 54 | 500 cc. of blood drawn |
| 8/ 7/44 | 6,500,000 | 100 | 17,800 | 59 | |
| 8/10/44 | 5,800,000 | 88 | 18,800 | 54 | |
| 8/17/44 | 5,000,000 | 88 | 14,900 | .. | |
| 8/18/44 | Right frontotemporal craniotomy | | | | |
| 8/21/44 | 3,700,000 | 68 | 16,400 | .. | |
| 8/24/44 | 3,800,000 | 75 | 15,000 | 43 | |
| 9/ 9/44 | ..... | 72 | 11,900 | .. | Patient discharged 9/12 |
| 10/ 7/44 | 5,600,000 | 98 | ..... | .. | |
| 12/14/44 | 6,700,000 (?) | 86 | ..... | .. | |
| 1/22/45 | 8,000,000 | 102.5 | 6,050 | 55 | Red cells showed achromia and microcytosis |

Lumbar puncture revealed that the fluid was clear and the pressure 350 mm. of water. There were 2,000 red blood cells per cubic millimeter. The protein measured 48 mg. per hundred cubic centimeters. The serologic reactions were negative; the colloidal gold curve was 0000000000. The roentgenogram of the skull was normal. A roentgenogram of the chest showed some enlargement of the right and left sides of the heart, with accentuation of the pulmonary markings.

Neurologic examination showed subjective numbness of the left arm and leg and the left side of the trunk. There was definite euphoria, with a tendency to memory defect and slowing of mental activity. The Romberg sign was positive, with swaying to the right. There was intention tremor in the heel to knee test. The knee and ankle jerks on the left side were greatly impaired. There was bilateral papilledema, with a few retinal hemorrhages. Objective sensory changes were confined


Fig. 1 (case 1).—Ventriculograms.

*A*, anteroposterior view, showing decreased filling of the right lateral ventricle with depression of the posterior portion of the body (indicated by arrow).

*B*, right lateral view. The depression of the posterior part of the ventricular body is shown by the arrows. This might well be considered a normal variant of the ventricle.

to the left side: They consisted of slight impairment of pain and temperature senses over the distribution of the trigeminal nerve (including a decreased corneal reflex) and downward to the fifth thoracic segment, moderate impairment of pain and temperature senses from the fifth to the tenth thoracic segment and complete loss of pain and temperature senses below the tenth thoracic segment. Position and touch senses were preserved bilaterally.

Consultation with the department of ophthalmology on July 23 showed that the patient's vision was 20/70 in the right eye and 20/60 in the left eye, without correction. There was crossed diplopia to the right,

indicating weakness of the left internal rectus muscle. The conjunctiva was normal. The disks showed choking of approximately 5 D. bilaterally. Veins were engorged over the disks but not excessively so in the surrounding fundi. There were a few scattered hemorrhages. The visual fields were full, with greatly enlarged blindspots. The impression was that there was an intracranial mass lesion with resulting choked disks. (Ophthalmoscopic examination on July 10 had shown papilledema, of 3 D. in the right eye and of 2 D. in the left eye.)

Medical consultation was obtained. It was the opinion of the consultant that while the patient had polycythemia this condition probably did not account for the high degree of choked disk or the bizarre neurologic findings. Turpentine fumes, to which the patient had been exposed for a number of years, were suggested as a possible cause of the polycythemia.

Because of the progression of symptoms, a ventriculographic examination was done under local anesthesia, on July 27. The occipital approach was used. Twenty cubic centimeters of clear fluid was obtained from the left lateral ventricle and 15 cc. from the right lateral ventricle. Dye passed readily between the two lateral ventricles. There was no ventricular shift, the only deviation from normal being apparent failure of the right lateral ventricle to fill as well as the left, with a questionable depression of the posterior part of the body of the right lateral ventricle (fig. 1). However, the change was so slight that it did not justify a diagnosis of tumor.

On August 2, 3 and 5, 500 cc. of blood was withdrawn by venipuncture. The results are seen in table 1. There was no apparent clinical improvement. Indeed, on August 15, visual acuity was 20/100 in the right eye and 20/70 in the left. Papilledema had increased to 6 D. bilaterally, and the visual fields showed definite suggestion of a left homonymous field cut (fig. 2*A*).

After further review of the case, a craniotomy was done in the right frontotemporal region on August 18 for exploration and decompression, in an effort to preserve vision. When the bone flap was turned back the dura was found to be light green. As the dura was opened, the neomembrane characteristic of chronic subdural hemorrhage appeared (fig. 3). The dura was further opened, and 15 to 20 cc. of coffee-colored fluid escaped. The rest of the clot, which was about 1 cm. thick and covered the posterior parietal area, was evacuated without difficulty. The region of the optic nerve was explored, only a few fine adhesions being found. A wide decompression was provided at the base of the flap; the dura was cut free, turned over and sutured into place. The bone flap was replaced and wired. A drain was inserted through a posterior stab wound, and the galea and skin were sutured with black silk. A trephine opening was made over the left parietal area, no evidence of hemorrhage being found. The postoperative course was completely uneventful.

On August 29, her visual acuity was 20/70 in the right eye and 20/60 in the left. Diplopia had disappeared, and the papilledema measured 4 D. on the right side and 3 D. on the left side. The visual fields

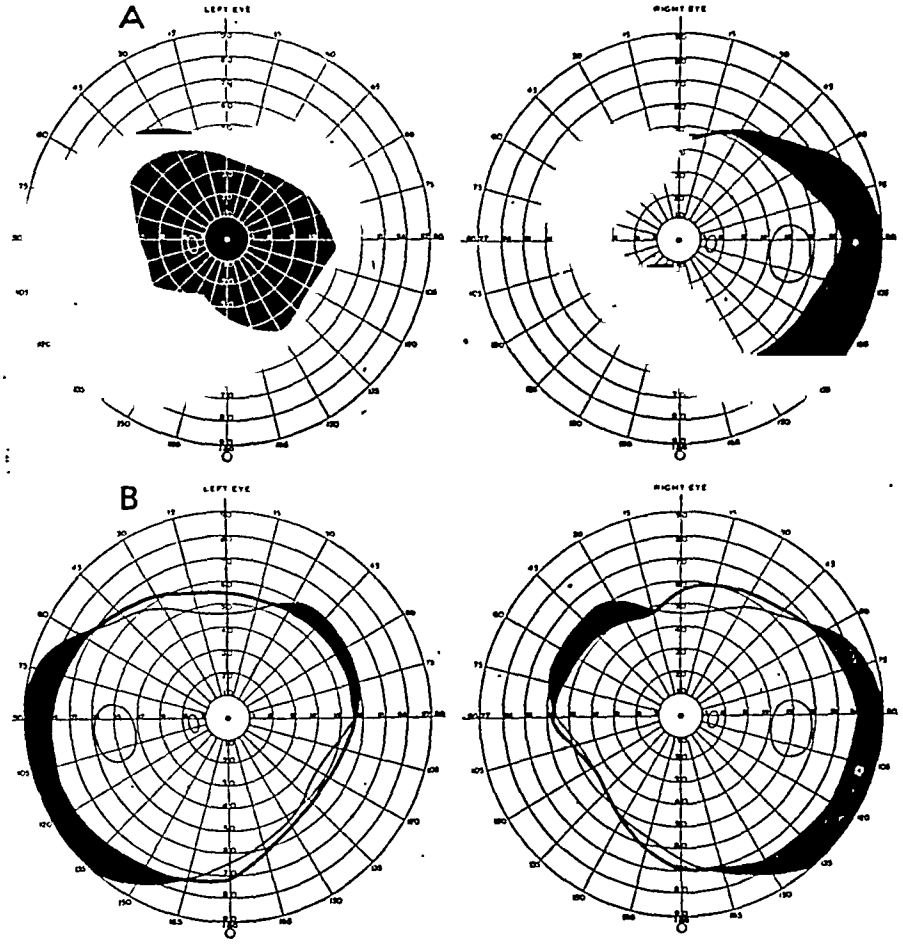



Fig. 2 (case 1).—Visual fields. *A*, fields before operation, showing generalized peripheral contraction with suggestive left incongruous homonymous hemianopsia.
*B*, fields after removal of subdural hematoma, showing normal peripheral vision.

showed notable improvement, with filling in of the defects noted in the previous examination.

The patient was discharged on September 12, with her condition much improved.

On September 22, her eyegrounds showed papilledema of less than 2 D. There was some fulness at the site of the decompression. She was last seen Jan. 22, 1945. The site of her decompression was soft but slightly tender. She had gained 10 pounds (4.5 Kg.) in weight and felt much better. She said her left leg and foot were still numb. Physical examination revealed nothing significant. Sensory examination revealed normal sensation for all modalities downward to the level of the tenth thoracic segment; there was moderate decrease of pain and temperature sensations to the level of the greater trochanter on the left side. Below this level, there was loss of pain and temperature sensations on the left side. Touch and position senses were preserved. There was slight weakness of the left lower extremity. The reflexes were physiologic.

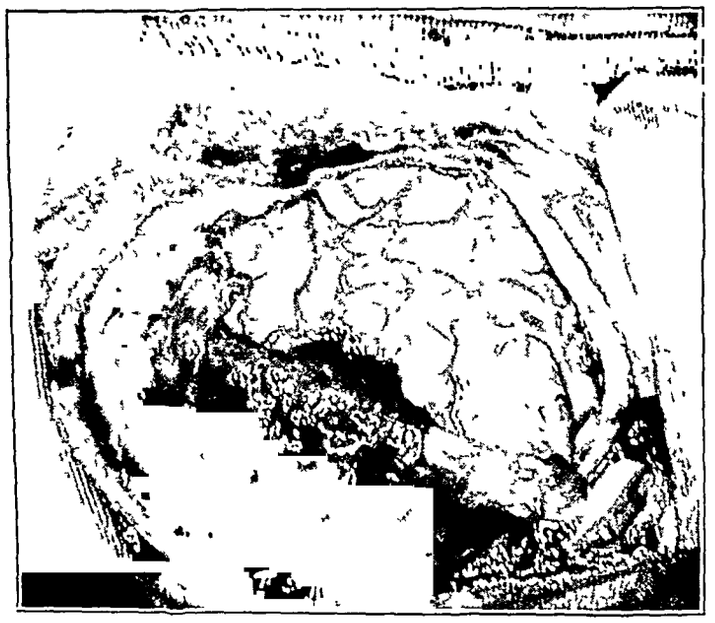


Fig. 3 (case 1).—Operative field. The large, chronic subdural hematoma is seen overlying the superior portion of the right parietal cortex. The temporal muscle, acting as a hinge for the bone flap, is at the top of the picture.

Ophthalmoscopic examination showed the nasal margin of the right disk to be blurred; the margin of the left disk was blurred throughout. There was questionable papilledema of 0.5 to 1 D. in each eye. The veins were not engorged, and the retina appeared normal. Visual acuity was 20/70 in the right eye and 20/100 in the left eye, without correction. With the pinhole disk it became 20/40 and 20/60, respectively. The visual fields were full; the blindspots were not enlarged (fig. 2*B*). Hematologic studies, the results of which are shown in table 1, indicated a beginning return of the polycythemia.

*Pathologic Study.*—The specimens removed at operation consisted of organized blood clot and membrane. Microscopically, the membrane consisted of fibrous tissue filled with small vascular channels, which were filled with red blood cells. It also contained many large mononuclear cells with homogeneously stained blue nuclei. The fibrous elements were mostly reticulin, with some collagenous fibers. Also, some fairly fresh blood clots were present. A small portion of the membrane had a better organized appearance and contained more fibroblastic cells, with fewer infiltrating blood cells. The diagnosis was membrane of a chronic subdural hematoma with cellular infiltration (*fig. 4*).

That this case was confusing is evident. The neurologic findings, the polycythemia, the papilledema and the normal ventriculogram all combined to make it extremely difficult to know what course to pursue. An operation was finally performed in an effort to preserve the patient's vision. The fact that a chronic subdural hematoma was found and removed, with notable improvement in the patient's symptoms, serves further to cloud the issue, since it is impossible to say whether the hematoma was caused by the minor head injury sustained in February, whether it was the result of hemorrhage due to polycythemia or whether it was the cause of the polycythemia. That it might be the result of hemorrhage from the polycythemia is suggested by the presence of fresh blood clots in the microscopic sections of the membrane. It is also of interest to note that the red blood cell count, which was somewhat low before operation, probably as the result of bleeding, fell notably after operation and remained low for approximately five months. This, again, suggests a possible relationship between the central nervous system and polycythemia.

In 1943, Tinney, Hall and Giffin [4h] reviewed the cases of 163 patients with polycythemia. Of these, 127 had signs referable to the central nervous system. In 2 of these "a cerebral neoplasm was actually found present." No further details are given. In this series, a tumor of the brain was suspected in only 8 cases. Galíndez and Sanguinetti [10] reported a case in which an "endothelioma" was found in the right frontal region at autopsy. The patient had weakness of the left arm and leg, bilateral papilledema (marked), a cerebrospinal fluid pressure of 500 mm. of water, a red blood cell count of 8,920,000 and a hemoglobin concentration of 125 per cent. Studies of the blood and bone marrow confirmed the case as one of polycythemia vera. With the case reported by us, there is a total of 10 reported cases in which an expanding intracranial mass lesion, not of the diencephalic area, was associated with polycythemia. No case has previously been reported in which chronic subdural hematoma was found with polycythemia.

The actual cause and effect relationship between lesions of the brain and polycythemia has never been definitely established, although the

10. Galíndez, L. V., and Sanguinetti, L.: Polyglobulia Vera with Right Frontal Tumor: Clinical and Anatomico-Pathologic Study of a Case, Rev. méd. latino-am. **19**:1055-1072 (July) 1934.

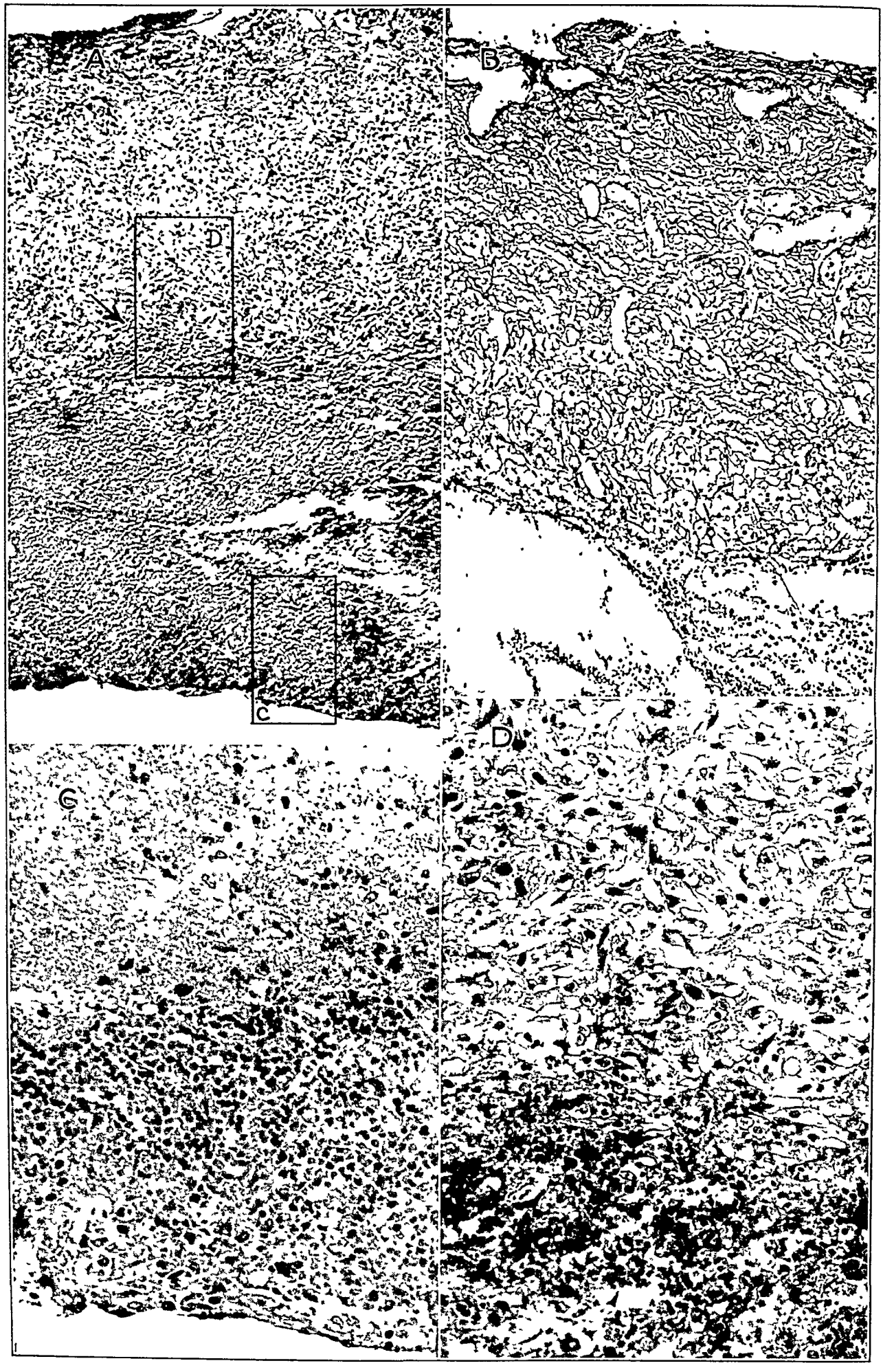



Figure 4

*(See legends on opposite page)*

feeling that it probably exists has been noted by a number of writers.[11] Other authors have stated that on the basis of clinical studies alone one must accept it as a distinct factor.[12] Carpenter, Schwartz and Walker,[5] in the conclusion of their paper, stated with regard to the polycythemia in their 2 cases: "We believe it to be of neurogenic origin." Excellent reviews on this phase of the subject are provided by several authors.[13] The experimental work done on animals[6g] is certainly suggestive but is not of sufficient volume to be conclusive at this time.

## PAPILLEDEMA AND POLYCYTHEMIA

The fundus picture which occurs with polycythemia is of particular interest in the effort to establish a differential factor for distinguishing between an intracranial mass and polycythemia as the cause of a given set of symptoms. This picture, which in the typical case is called "fundus polycythemicus," is well recognized and quite characteristic. It has been described in considerable detail by many writers, including de Schweinitz and Woods.[14]

> The usual fundus picture of polycythemia, if there is a characteristic fundus picture, consists of dilatation, sometimes uneven, of retinal veins, and deepening of their color, and alterations, cyanotic in type, of the normal color of the eyegrounds, without hemorrhages, or exudates or changes in the optic nerve, and generally without marked change in the caliber of the arteries.

These authors also noted that blurring of the margins of the disks may often occur. Venous dilatation becomes pronounced when the hemoglobin concentration is 110 per cent or more, and retinal cyanosis occurs only when the hemoglobin content exceeds 125 per cent. Weber[15] also discussed this picture in considerable detail. In all the 13 cases at this hospital in which the presence of severe neurologic signs was previously mentioned, full purplish veins were noted; in 5 the margins of the disks were pathologically blurred, and in 1 the disk was almost obliterated by hemorrhages. In another case, in which the patient died one week after admission and in which cerebellar impaction was found at autopsy, there was only venous distention. Papilledema was not noted in any case.

In 1929, Brockbank[4b] reviewed 56 cases of polycythemia, in only 1 of which papilledema was present but in all of which definite neurologic damage existed. Adams[4a] reviewed 9 cases "with special reference to nervous manifestations" and did not mention papilledema as occurring in any. Dameshek and Henstell[16] and Fucher[4d] gave excellent discussions of polycythemia as a general medical problem but did not bring choked disk into the picture. On the other hand, Weber[15] stated:

> Probably the ophthalmoscopic changes of "cyanosis retinae" may progress to choked disc and typical optic neuritis, not only in ("primary") erythremia, but in cases of chronic cyanosis with secondary polycythemia when of cardio-vascular origin.

Duke-Elder[17] stated that there may be "oedema of the disc, which may even simulate papilledema due to cerebral tumour." With these statements in mind, we felt that a review of the existing literature, with the addition of a case of our own, would be worth while.

CASE 2.—E. C., a 49 year old white laborer, was admitted to the neurosurgical service of the Hospital of the University of Pennsylvania on Oct. 23, 1940, complaining of loss of vision, diplopia and chronic headache.

The patient, a chronic alcoholic addict, had been in his usual state of health until August 1940, when he began to suffer from generalized headaches, which became progressively more frequent and severe until finally they became constant. Two weeks after the onset of headaches, he noticed beginning failure of vision. This was followed by diplopia, which became more pronounced. His vision on admission was so poor that he was unable to read a newspaper. He had been slightly deaf in the right ear since 1930.

11. Baserga.[6a] Guillain, Lechelle and Garcin.[6f] Salus.[6g]

12. Castex,[6c] Da Rin and Costa.[6d] Ferraro and Sherwood.[6e]

13. Carpenter, Schwartz and Walker.[5] Castex.[6c] Da Rin and Costa.[6d] Ferraro and Sherwood.[6e]

14. de Schweinitz, G. E., and Woods, A. C.: Concerning the Ocular Symptoms of Erythremia (Chronic Polycythemia Vera) with Special Reference to the Fundus Picture, Tr. Am. Ophth. Soc. **23**:90-105, 1925.

15. Weber, F. P.: Polycythemia, Erythrocytosis, and Erythremia, London, H. K. Lewis & Co., Ltd., 1921, p. 82.

16. Dameshek, W., and Henstell, H. H.: The Diagnosis of Polycythemia, Ann. Int. Med. **13**:1360-1388 (Feb.) 1940.

17. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1941, vol. 3, pp. 2738-2739.

EXPLANATIONS OF FIGURE 4

Fig. 4 (case 1).—Membrane of chronic subdural hematoma. *A*, low power, showing fibrous outer membrane overlying organizing blood clot, which contained many fresh red blood cells (arrows). Hematoxylin and eosin stain; × 75. *B*, outer membrane, showing fibrous structure. Wilder stain; × 150. *C*, margin of hemorrhagic layer, with large mass of fresh red blood cells in the midst of the older clot. Hematoxylin and eosin stain; × 330. *D*, junction of the fibrous and the hemorrhagic layer, showing mass of fresh red blood cells. Hematoxylin and eosin stain; × 280.

About Sept. 10, 1940, he first noticed tinnitus in both ears. He had lost considerable weight (exact amount not known) and was "run down."

Physical examination showed that the patient was emaciated but not acutely ill. His skin was warm and dry and had a ruddy, cyanotic color. The left eye was slightly more prominent than the right. There was moderate conjunctival congestion. Hearing was grossly impaired in the right ear, bone conduction being greater than air conduction, with sound localized to the right in the Weber test. The mucous membrane of the mouth and pharynx was not injected or cyanotic. The lungs had occasional, scattered rales throughout. The heart was not enlarged; there was an apical systolic murmur. The liver was questionably palpable on deep inspiration; the spleen was not palpable. The extremities showed emaciation but no localized weakness. The blood pressure was 136 systolic and 88 diastolic when the patient was in the supine position. Urinalysis revealed nothing abnormal. The Kolmer and Kahn reactions of the blood were negative; the plasma protein measured 6.9 Gm. per hundred cubic centimeters, and the chlorides, 97.7 milliequivalents. The hematologic findings are listed in table 2.

TABLE 2.—*Hematologic Findings in Case 2*

| Date | Red Cells (Cu. Mm.) | Hemoglobin, % | White Cells (Cu. Mm.) | Miscellaneous Data and Treatment |
|---|---|---|---|---|
| 10/24/40 | 8,880,000 | 140 | 10,800 | Hematocrit reading, 72; volume index, 0.88 |
| 11/ 6/40 | 8,250,000 | 134 | 7,500 | |
| 11/ 7/40 | 9,000,000 | 144 | 12,400 | |
| 11/11/40 | 7,400,000 | 136 | 12,000 | 1,000 cc. of blood drawn |
| 11/13/40 | 8,100,000 | 118 | 11,100 | Hematocrit reading, 61; volume index, 0.80 |
| 11/18/40 | Right frontoparietal craniotomy | | | Transfusion of 1,000 cc. of blood |
| 11/21/40 | 4,400,000 | 76 | 17,000 | |
| 11/27/40 | 3,800,000 | 73 | 9,700 | |
| 12/ 2/40 | 4,500,000 | 75 | 18,300 | Patient discharged 12/20 |
| 3/12/41 | 5,000,000 | 96 | ..... | |
| 6/13/41 | ..... | 105 | ..... | |
| 9/16/41 | 7,900,000 | 116 | 8,200 | |

Lumbar puncture revealed that the fluid was xanthochromic and the pressure 510 mm. of water. There were 130 red blood cells and 30 white blood cells (20 polymorphonuclear leukocytes, 10 mononuclear cells) per cubic millimeter. The protein measured 50 mg. per hundred cubic centimeters. The serologic reactions were negative; the colloidal gold curve was 0000000000. Roentgenograms of the chest and skull were normal.

Neurologic examination showed the motor and sensory systems to be intact. There were horizontal nystagmoid movements to the right and to the left and pronounced bilateral papilledema with hemorrhages. The reflexes were physiologic. There was some tremor on both sides on performance of the finger to nose test.

The patient was seen in consultation by members of the medical service, and their feeling was that all his symptoms might be accounted for on the basis of his polycythemia. Phlebotomy was suggested as a means of preventing further progression of the process. One thousand cubic centimeters of blood was withdrawn, without change in his symptoms.

Because of his visual complaints and the obvious pathologic condition in his eyes, the department of ophthalmology was asked to see the patient, on October 24. Visual acuity was 10/200 in the right eye and 20/200 in the left eye. The external examination revealed an essential normal condition. The ophthalmoscopic examination showed that the right disk was elevated 7 D., the papilledema being of the collar button type, with encroachment on the macular area. There were few macular bands; no star-shaped figure was present. The veins were engorged, and there were a few scattered hemorrhages and exudates about the nerve head. The peripheral portion of the retina was normal. The left eye was similar to the right except that the papilledema measured 5 D. Both central visual fields showed enlarged blindspots. The papilledema gradually decreased until, on Nov. 4, 1940, it was only 4 D. in each eye and was more diffuse. On November 11, two days after the withdrawal of 1,000 cc. of blood, the right eye showed 3 D. of choking with many hemorrhages, and the left eye, 4.5 D. of choking with hemorrhages around the disk.

Opinion was divided as to whether the signs and symptoms were due to polycythemia or to an intracranial mass, the immediate problem being the preservation of vision. The papilledema did not decrease after the initial change; because of this, it was decided that at least a decompression should be done to relieve the increased intracranial pressure.

On November 18, under local anesthesia, the lateral ventricles were tapped by the occipital route, and considerable pressure was encountered. The left lateral ventricle contained 35 cc. of fluid; the right lateral ventricle contained only 3 to 4 cc. In view of these findings and the absence of localizing neurologic signs, the possibility of a tumor in the right frontal lobe was considered and a craniotomy in the right frontoparietal region was immediately done, under local anesthesia.

When the bone flap was turned back, the dura, rather than being tense, as might have been expected from the pressure found when the ventricles were tapped, was notably relaxed. It was opened from below upward, revealing marked cortical atrophy. The sulci were full of fluid, and the surface of the cortex was covered with a semiopaque membrane. This was incised and considerable clear fluid allowed to drain out, thus accentuating the atrophy of the cortex. There was obviously no tumor present; so the dura was free grafted, sutured and drawn up to the bone, after all bleeding points had been secured. The dura was left open at the base to provide a wide decompression. The bone was replaced and wired, and the galea and skin were closed with black silk, without drainage

After operation the patient received phenobarbital, ½ grain (0.032 Gm.), to forestall possible convulsions. He was drowsy; so this medication was discontinued on November 24. On November 25 weakness developed on the left side, which became paralysis on the following day. On November 27, he had a clonic convulsion of the left arm and leg. He was once more given phenobarbital, and no more convulsive attacks occurred. On November 29, he was moved into a wheel chair, and from then on his convalescence was smooth.

The ophthalmologic examination, sixteen days after operation, showed, on the right, beginning optic nerve atrophy and 4 D. of papilledema. The fundus was much paler than before operation, and the veins were thinner and not dark or engorged. There were a few scattered hemorrhages. On the left the papilledema was 3 D., the rest of the picture being similar to that seen on the right. The impression at this time was retinal anemia, bilateral papilledema and secondary optic nerve atrophy.

The patient was discharged on Dec. 20, 1940, with instruction to return to the outpatient department.

On March 21, 1941, he was again seen. The red blood cell count was 5,000,000, and the hemoglobin concentration, 96 per cent. There was no vision in the right eye. Vision in the left eye was 20/80, with a full peripheral field. Subjectively, he was much better. On June 16, 1941, he showed considerable improvement. Vision was 20/40 in the left eye and was limited to perception of fingers at 5 feet (152 cm.) in the right eye. Perimetric examination showed a full visual field on the left and moderate contraction on the right (fig. 5). No measurable papilledema was present. There was bilateral secondary optic nerve atrophy. The hemoglobin concentration was 105 per cent. Neurologic examination failed to show any residual weakness on the left side. On Sept. 10, 1941, he returned, complaining of "loss of pep." Vision was unchanged. There was bilateral optic nerve atrophy, with choking of 1 to 2 D. on the right side and 1.5 to 2 D. on the left side. The reflexes were hyperactive. No pathologic reflexes were present. The red blood cell count was 7,900,000; the hemoglobin content, 116 per cent. The patient died at his home Jan. 17, 1942; no further details were available.

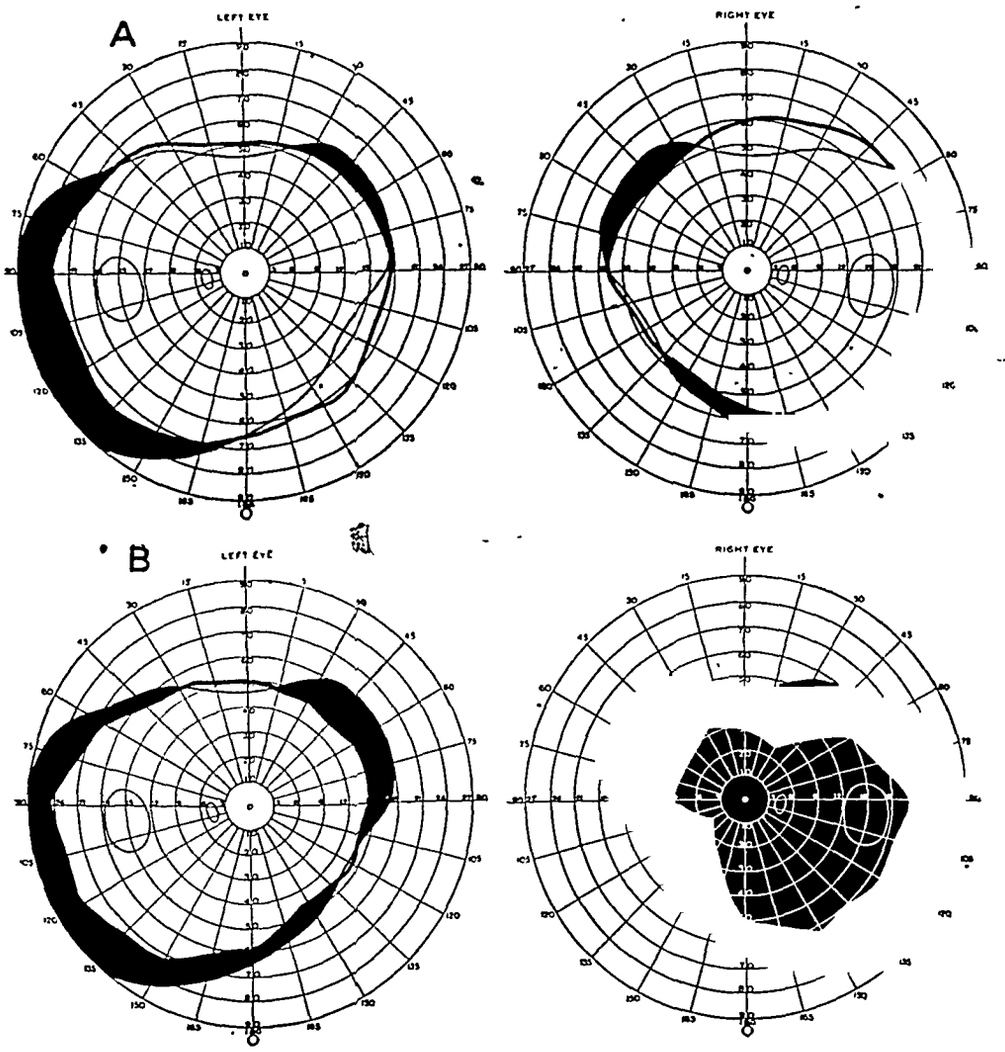



Fig. 5 (case 2).—Visual fields. *A*, before operation. The central fields showed notable enlargement of the blindspots. *B*, after operation: The right field was definitely contracted. Visual acuity, however, was improved, especially in the left eye.

Diagnostically, this case presented a real problem. It was the opinion of members of the medical department that all symptoms could be accounted for on the basis of polycythemia. On the other hand, the ophthalmologists expressed the belief that the papilledema was of too great a degree to be compatible with such an explanation. In the meantime, though the papilledema became less pronounced, vision did not improve, and optic nerve atrophy began to develop. The neurosurgical service, faced with these conflicting opinions and facts, felt that the least that could be attempted was a decompression, in an effort to preserve as much vision as possible. This was done, with negative results as far as finding a tumor was concerned and with indifferent results from the standpoint of preserving vision. It is extremely interesting to note that immediately after operation, and for eight months thereafter, the hemoglobin level stayed within or below normal limits. Only three months before the patient's death did it begin to rise.

As far as we are able to determine, a total of 17 cases of polycythemia have been reported in which the optic disks showed changes which may be considered as papilledema or choked disk (exclusive of cases in which polycythemia was associated with an expanding intracranial mass). This review includes Knapp's [18] case, described

18. Knapp: A Case of Hyperemia of the Retina with Choked Disc, Verhandl. d. naturh.-med. Ver. zu Heidelberg **2**:84-86, 1859-1862.

before polycythemia was recognized, which Kümmel [19] believed to be one of polycythemia.

Russell,[20] in 1906, reported "a case of cyanosis with polycythemia" in which the red blood cell count was as high as 8,650,000 (hemoglobin, 120 per cent) and the disks showed "considerable blurring of the edges, obviously due to edema." Whether the "blurring" and "edema" were of the type considered now to be a relatively frequent finding in the polycythemic fundus, or whether there was true papilledema, is open to question. Lucas [4f] evidently felt they were not significant, since he flatly stated that his and Pfeiffer's [21] cases were the only ones with papilledema reported up to the time of his review, in 1912. Pfeiffer's [21] patient had frontoparietooccipital headache. The liver and spleen were bilateral choking of 2 D. Lucas [4f] reviewed 189 reported cases of polycythemia and added 2 of his own. In his first case there was concentric contraction of the visual fields, with 4 D. of papilledema bilaterally. The report on the eyegrounds stated that the "changes are those of typical inflammatory choked disk, identical, it would seem, with those frequently seen with intracranial disturbance." The patient complained of headache and blurred vision. The red blood cell count ranged from 5,200,000 (hemoglobin, 96 per cent), after bleeding, to 8,660,000 (hemoglobin, 140 per cent), before bleeding.

Christian [1c] cited the case of a patient who complained of poor vision, tingling in the left arm and leg and left hemiparesis. He had left homonymous hemianopsia, a positive Babinski

TABLE 3.—*Reported Cases of Polycythemia Associated with Papilledema Exclusive of Those with Intracranial Mass**

| Author(s) | Year | Classification According to Author: Edema | Classification According to Author: Choking (Papilledema) | Amount (D.) of Papilledema | Comment |
|---|---|---|---|---|---|
| Knapp | 1859 | .. | + | Not given | Polycythemia probably present |
| Russell | 1906 | + | .. | Not given | Blurring of edges, obviously due to edema, according to author |
| Pfeiffer | 1907 | .. | + | Not given | Moderate choked disk |
| Lucas | 1912 | .. | + | 4 | |
| Christian | 1917 | + | .. | Not given | |
| Cohen | 1918 | .. | + | 3 | Papilledema of nasal margin of left papilla only |
| Redlich | 1920 | .. | + | Not given | Slight choking |
| Nueda | 1922 | .. | + | Not given | |
| Moore | 1922 | .. | .. | ..... | Changes in disks little different from those of cerebral tumor |
| Horder | 1926 | .. | + | 2 and 5 | |
| Oppenheimer | 1929 | .. | .. | ..... | Operation for suspected brain tumor; patient probably had papilledema |
| Brockbank | 1929 | .. | + | Not given | Right eye only; operation for intracranial mass |
| Cohen | 1937 | + | .. | Not given | Diagnosis: fundus polycythemicus with edema of disk |
| Tinney, Hall and Giffin | 1943 | .. | + (4 cases) | Not given | In 2 cases intracranial mass probably present |
| Lowman, L., and Dameshek, W.: New England J. Med. **232**: 394-397 (April 5) 1945 | 1945 | .. | + | Not given | Choking of disks, particularly over nasal halves |
| Drew and Grant | 1945 | .. | + | 5 and 7 | Operation for suspected brain tumor |

* For 2 possible exceptions see table.

not enlarged. The red blood cell count at its highest point was 10,040,000; at the lowest, 5,968,400. The hemoglobin values ranged from 155 to 100 per cent. The eyegrounds showed "moderate" choked disks with vague margins. The cerebrospinal fluid pressure on lumbar puncture was 370 mm. of water. In this same case, as reported later by Behr,[22] there was sign on the left, "blindspots in the field of vision" (scotomas?) and edema of the disks (amount not stated). For ten years it had been suspected that he had a tumor of the brain. A "cerebral decompression" was done. He subsequently died. Autopsy showed bilateral thrombosis of cerebral arteries with cortical degeneration.

Cohen,[23] in 1918, reported a case in which there was a two year history of failing vision in the right eye and hot flushes. There were plethora, cyanosis and enlargement of the liver and spleen. The red blood cell count ranged from 8,000,000 to 10,000,000, and the hemoglobin level, from 140 to 160 per cent. The Wassermann reaction of the blood was strongly

19. Kümmel, U., in Schieck, F., and Brückner, A.: Kurzes Handbuch der Ophthalmologie, Berlin, Julius Springer, 1931, vol. 7, p. 74.

20. Russell, J. W.: A Case of Cyanosis with Polycythemia, Lancet **2**:20-21 (July 7) 1906.

21. Pfeiffer, W.: A Case of Polycythemia Without Splenomegaly, Deutsches Arch. f. klin. Med. **90**:609-617 (July) 1907.

22. Behr, C.: The Nature of the Ocular Changes in Polycythemia Together with a Contribution on the Theory of Choked Disc, Klin. Monatsbl. f. Augenh. **48**:672-688, 1911.

23. Cohen, M.: Eye Manifestations in a Case of Polycythemia, Arch. Ophth. **47**:192-194 (March) 1918.

positive. Examination two years previous to the patient's admission showed a typical fundus polycythemicus. On admission, the patient had no vision in the right eye, and the nasal margin of the right papilla was blurred. The left disk was yellowish white on the temporal side, with a sharp outline. The nasal margin showed papilledema of 3 D.

A case of erythremia with a red blood cell count of 7,200,000 (hemoglobin, 115 per cent), enlarged spleen and liver, cyanosis and "slightly" choked disks was reported by Redlich.[24]

Nueda [25] reported a case in which were present cyanosis, enlarged spleen and liver and a red blood cell count of 7,000,000 to 8,000,000. He particularly called attention to the choked disk, which he said was rare in cases of polycythemia. The cerebrospinal fluid pressure in this case was 300 mm. of water.

Moore [26] mentioned a case in which "the disc changes differed little from the papilloedema of a cerebral tumor."

Seven cases of polycythemia with neurologic complications were discussed by Horder.[4e] One of the patients (case 4) had headache and stiff neck fifteen months before her admission. She also complained of blurred vision and occasional diplopia. Nine months previous to admission she noticed impaired sense of smell and intervals of blindness. She was cherry red and cyanotic. The spleen was not palpable. The red blood cell count was 6,320,000 (hemoglobin, 100 per cent). The hemoglobin level eventually reached 134 per cent. Notes on the eyegrounds stated: "The disc edges are greatly obscured; the discs themselves are swollen about 2-5 D." Five months later the changes in the disks were indistinguishable from those seen with a cerebral neoplasm.

The 1 patient whom Brockbank [4b] mentioned as having papilledema came to him with a history of having had choked disk in the right eye two years previously, although none was present at the time of Brockbank's examination. The patient had sustained a previous head injury, after which he had failing vision. Chronic polycythemia developed four months after the accident, the red blood cell count being 6,400,000 (hemoglobin, 108 per cent). On the basis of the visual changes and the results of ventriculographic studies, operation for a suspected intracranial lesion was carried out, but nothing was found. Cohen,[27] in 1937, reviewed 7 cases of polycythemia and discussed the ophthalmic findings. In 1 of these (case 5) there was a red blood cell count of 7,800,000 (hemoglobin, 140 per cent) and "edema" of the disk—the amount not being given.

Tinney, Hall and Giffin,[4h] in their review previously mentioned, reported choked disks in 4 of 163 cases. The amount of choking was not stated, nor was it indicated whether these 4 cases included the 2 mentioned earlier as instances of cerebral tumor, although this is probable.

To the aforementioned series may be added the case cited by Oppenheimer.[8] The patient had paresthesias on the right side with hemiparesis of the same side and aphasia. He was operated on for suspected tumor of the brain, with negative results. There is no mention of papilledema or of the eventual outcome of the case. The only other case in which operation was done was that reported by Adams.[4a] The patient had fainting spells and convulsions after a bad injury. Roentgenograms of the skull and air studies revealed nothing significant. The red blood cell count was 9,500,000 (hemoglobin, 145 per cent). The patient was later operated on in Norway for traumatic epilepsy, with negative results. He had a severe postoperative hemorrhage.

The 19 cases of polycythemia presumed to be associated with papilledema (table 3) may be analyzed as follows:

1. One case was reported before polycythemia was recognized, and the diagnosis must be on a presumptive basis.

2. In 2 cases papilledema may be assumed to have existed, since in 1 case ocular changes were present similar to those found with brain tumor and in the other operation for suspected cerebral tumor was performed.

3. In 2 cases papilledema was noted in only one eye, and in 1 of these on only the nasal margin of the disk.

4. In 3 cases the changes were referred to as "edema of the disk," rather than as choking or papilledema.

5. In 13 cases choking or papilledema occurred as such, but in 2 of these there was probably an associated tumor of the brain.

6. Of the 13 cases, the amount of papilledema was stated in only 4, the range being 2 to 7 D.

24. Redlich, F.: Erythremia (Polyglobulia) and Erythromelalgia, Wien. med. Wchnschr. **70**:959-962 (May 15) 1920.

25. Nueda, P.: A Case of Erythremia (Vaquez) with Erythromelalgia with Choked Disc, Wien. med. Wchnschr. **72**:533 (March 18) 1922.

26. Moore, R. F.: Medical Ophthalmology, ed. 1, London, J. & A. Churchill, 1922, p. 82.

27. Cohen, M.: Lesion of the Fundus in Polycythemia Arch. Ophth. **17**:811-818 (May) 1937.

7. In 3 cases operation was performed for a suspected intracranial mass lesion, with negative results.

From those facts, it is evident that while papilledema can and does occur in association with, and as the result of, polycythemia, it is not a common finding, and, indeed, may be considered as an unusual complication. Because of the tendency for signs and symptoms referable to the central nervous system to develop with this disease, the association of papilledema with these changes may present a real and serious neurosurgical problem. If intracranial disease, including expanding mass lesions, is further considered as a possible cause of polycythemia, one is confronted with something more than the usual questions involving diagnosis and treatment. There is a growing volume of literature in support of the latter relationship, and the neurosurgeon must be prepared to recognize and cope with situations of this type.

## SUMMARY AND CONCLUSIONS

The importance of polycythemia as a differential problem in neurosurgery is real. Complications referable to the central nervous system in cases of polycythemia are extremely frequent, and recognition is accorded the growing number of such cases. In the first case presented, chronic subdural hematoma was associated with polycythemia, which disappeared after removal of the hematoma but showed a tendency to return five months after operation. A review of the literature concerned with the coincident occurrence of expanding intracranial mass lesions and polycythemia revealed 9 cases in which the diencephalic region was not involved. A brief discussion of the "usual" fundus picture of polycythemia is given. In the second case presented, papilledema of high degree was associated with polycythemia, and the existing literature on this relationship is reviewed.

It may be concluded that the occurrence of a true expanding intracranial mass lesion with *polycythemia is rare but that the coincident occurrence* of papilledema and polycythemia is somewhat more common. However, this association is not as frequent as might be suspected from casual comments in the literature. The cause and effect relationship between polycythemia and disease of central nervous system is becoming increasingly well documented, but the volume of work done is not yet sufficient to warrant its being recognized as an established fact.

Polycythemia with papilledema must be considered as a possible diagnostic and operative problem for the neurosurgeon.

# HYPOTHALAMIC ATTACKS WITH THALAMIC LESION

## I. PHYSIOLOGIC AND PSYCHOLOGIC CONSIDERATIONS

GEORGE L. ENGEL, M.D., AND CHARLES D. ARING, M.D.
CINCINNATI

The functions of the hypothalamus have been elucidated by the careful studies of Bard, Fulton, Long, Masserman, Ranson, Sheehan and their co-workers on animals.[1] Observations on patients with structural lesions of the hypothalamus have amply confirmed these studies. Most of the clinical examples, however, have been concerned with destructive lesions of some portion of the hypothalamus and, consequently, with more or less static disturbances of function, such as diabetes insipidus, hyperthermia and hypothermia, etc. More unusual have been cases in which periodic massive discharges of hypothalamic activity have taken place, such as the case of a ball valve tumor of the third ventricle reported by Penfield.[2]

To our knowledge, there is no report of a destructive and fixed lesion outside the hypothalamus leading to disturbance of hypothalamic function with repeated display of exaggerated hypothalamic activity. The present case represents such an example; a cystic, degenerative lesion involving chiefly the dorsomedial and lateral nuclei of the right thalamus, apparently acquired at birth, was associated with repeated paroxysms of hypothalamic overactivity, the final attack terminating in death in the eighteenth year. The location of this small lesion was such as probably to interrupt some corticohypothalamic association fibers. The hypothalamus itself was intact.

The minute neuroanatomic lesion was in itself not sufficient to explain the clinical picture. An adequate understanding of the dynamics of the case became possible only after proper consideration of certain essential physiologic and psychologic factors.

From the Departments of Psychiatry and Medicine (Neurology) of the University of Cincinnati College of Medicine, and the Cincinnati General Hospital.

1. (*a*) Fulton, J. F.: Physiology of the Nervous System, ed. 2, New York, Oxford University Press, 1943, p. 614. (*b*) The Hypothalamus, Proceedings of the Association for Research in Nervous and Mental Diseases, Baltimore, Williams & Wilkins Company, 1940, vol. 20.

2. Penfield, W. G.: Diencephalic Autonomic Epilepsy, Arch. Neurol. & Psychiat. **22**:358-374 (Aug.) 1929.

### PHYSIOPATHOLOGIC STUDY

The patient was a white youth 17¾ years of age at the time of his death. He had been born prematurely and weighed 5 pounds 5 ounces (2,410 Gm.) at birth. Birth was uneventful, and at delivery the infant appeared to be in good condition. The pregnancy had been normal except that the mother suffered from repeated urticaria during the early months of gestation. Copious administration of epinephrine resulted in symptomatic relief.

On the third day of life the infant had a "blue spell." This marked the first of a series of different types of episodes which occurred repeatedly throughout his life. Until the age of 13 the boy experienced numerous spells in which he was said to hold his breath, become cyanotic and lose consciousness. It is estimated that he had between 125 and 150 of these spells, which occurred less frequently in later years, and not after the age of 12 years. Occasionally he would have them during his sleep. It was thought that the attacks were precipitated by crossing the child, and he was known to have them on passing a cemetery, which he did not like to enter. Abandoned laughter precipitated attacks. In these episodes his head would be thrown backward, and he would lapse into unconsciousness. The extremities would extend and the hands pronate. He was not incontinent. An attack would last less than a minute and was followed by deep sleep. He never had a clonic convulsion. Because of the episodes of "breath holding," the thymus gland was examined roentgenographically in infancy and was found to be enlarged. He was given an occasional irradiation over the thymus, the last at the age of 5 or 6 years, when he had received a total of twenty treatments.

At the age of 5 months a second type of attack had its inception, the final one of which was associated with his death. Over the course of the years there had occurred 15 to 20 of these episodes. All the attacks followed essentially the same pattern, although they differed somewhat in intensity and duration. The attack was usually ushered in by what appeared to be rhinitis. With the onset of the attack he complained of coldness, shivered and sometimes had a chill. The face and extremities were noted to be cold and pale, while the trunk was warm. Sweating was absent in this phase. The presence or absence of piloerection was not noted in any of the records. During this period the rectal temperature rose rather abruptly in the course of a few hours to 105 or 106 F. The pulse was rapid, while the blood pressure, though fluctuating between moderate hypertension and hypotension, usually tended to fall. The patient appeared critically ill in this phase. Rales were heard in the chest. The rectal temperature usually remained elevated several hours and then would suddenly fall. The sudden defervescence was marked by profuse sweating and flushing of the trunk and extremities. Rapid swings of temperature then occurred for the next three to four days, the temperature tending toward nor-

mal with the passage of time. It was unusual to find the temperature the same on any two successive readings, taken as frequently as one-half to one hour apart, and he sometimes had a number of spikes daily. Later it was found that the attacks and fever could be aborted by pentobarbital sodium, as well as by the usual antipyretics.

All the attacks were accompanied with evidence of pronounced gastrointestinal overactivity. The patient experienced severe cramps, nausea and vomiting and was unable to retain food for several days. Occasionally the vomitus contained blood. Sometimes the vomiting persisted longer than the disturbances in temperature and once lasted ten days. Diarrhea also accompanied some of the attacks.

During the attacks there was usually oliguria; the urine was concentrated and contained albumin and hyaline and granular casts. Evidences of hemoconcentration were present. The blood urea nitrogen rose, on one occasion reaching 88 mg. per hundred cubic centimeters. With recovery, the urine rapidly returned to normal except for the presence of casts, which persisted until the age of 13 and then disappeared, to reappear with the feverish attacks. In routine urinalyses the specific gravity ranged from 1.010 to 1.025. The white cell count was usually normal during an attack. All the episodes were associated with severe cramplike pains in the arms and legs. It was thought that these might have been related to the excessive vomiting.

With each attack he lost 8 to 10 pounds (3.6 to 4.5 Kg.) but regained this weight quickly. The attacks were terminated by the unexpected announcement that he again felt well.

His family, which included an intelligent, observant physician (his father), noted that the attack of fever always followed excitement or tension. Contemplation of an impending examination in school was probably the most frequent offender, although the attacks had occurred after the excitement of attending a football game, or precedent to a trip or before coming home after a period away from it. Intercurrent infections, such as measles and chickenpox, were associated with excessive rises in temperature, and the boy was critically ill with each infection.

An incidental observation was that the eyes never teared during crying. He suffered from enuresis up to the age of 4 years. He was always considered to have a degree of muscular incoordination. He was unable to swim; he could not run, though he played at basketball, and he was rather adept at the piano. In his final summer it was observed that he staggered for several minutes after alighting from a subway train or on coming out of darkness into the light or out of light into darkness. The latter situation was particularly disabling. It appeared as though he could not adjust readily to any rapid change and this was one of them. Loud noises frightened him, and he was always considered to suffer from "vasomotor instability." When he perspired, it was noted that the left side of the forehead, and not the right, was covered with beads of perspiration.

Throughout his life the boy suffered from attacks of bronchial asthma. He had cutaneous tests for all the common foods at the age of 7 and was found to react positively to almost all of them. However, his diet was not restricted, and no clear association between food and the asthmatic attacks was ever demonstrated.

He had all sorts of medication for his various symptoms—among others, glandular therapy. Administration of chorionic gonadotropin at the age of 12 was associated with descent of the left testicle after the third injection.

An incidental observation was his pronounced fondness for hot foods, particularly for soups—foods that would upset him. His parents would request him not to take hot foods. During their eating he would perspire obviously on the left side of the forehead, and after ingestion he would become pale and dizzy and occasionally have to lie down for a short time.

As an infant he presented a difficult feeding problem, but at the age of 1 year he weighed 15 pounds (6.8 Kg.). Despite a voracious appetite he never seemed to gain weight normally. Eleven months before death, when nearly 17 years old, he was 4 feet 11 inches (149.9 cm.) tall and weighed 76 pounds (34.5 Kg.). He was generally underdeveloped, showing a small skeleton and poorly developed muscles. The penis and testicles were small, and the changes of puberty had not appeared. The underdevelopment was symmetric. Bone age was normal. His appearance essentially was that of a symmetric dwarf, since the underdevelopment seemed to involve the skeleton as well as the muscles.

The abnormal neurologic signs at the age of 17 years were as follows: The retinal arteries were tortuous. The eyes did not converge. There was weakness about the mouth; when he was asked to show the teeth, the upper lip was drawn laterally, the lower lip moving little, if at all. Speech was of the bulbar type, guttural in sound, as though the mouth were full. There was some drooling of saliva. He could not whistle. He was left handed, while the members of his family were right handed. Muscular development was retarded, and all movements lacked vigor. Breathing was largely diaphragmatic, since the intercostal muscles did not appear to move. There were lordosis of the lumbar portion of the spine and scoliosis of the dorsal portion. Resistance to passive movements was generally reduced. The range of passive movement of the joints was limited, and one could not flex or extend them completely. He could not raise the hands above the head. He walked stiffly, with the legs apart, weaving rarely to either side, the trunk bowed forward somewhat. It was impossible to obtain any of the deep reflexes.

He attended high school and took part in modified physical activities. He was bedfast only during the feverish episodes, the last of which had its onset ten days before death. He had taken his midsemester examinations. There then began the usual rhinitis, and on the eighth day the usual vomiting and abdominal cramping. The vomiting became retching, and the temperature ascended sharply to 103 F. As always during these attacks, he appeared desperately ill. Pentobarbital sodium, which had ameliorated some of the previous feverish attacks, failed to be effective. His temperature rose to 107 F. About twelve hours before death he was given morphine sulfate, ⅛ grain (8 mg.), after which he could never be aroused. This was thought to be the first dose of morphine that he had ever had. He ceased to excrete urine. Rales appeared in the chest, and he died.

*Laboratory Data.*—Psychologic examinations revealed intelligence quotients of 99 at the age of 5 years, 92 at the age of 6 years and 88 at the age of 13 years. Blood counts were normal. Reactions of the blood to the Wassermann and Kahn tests were negative. At the age of 6 years the sugar and the nonprotein nitrogen content of the blood were normal. Numerous roentgenographic studies of the chest and the gastroenteric tract showed nothing abnormal.

The blood pressure varied tremendously. Determinations during a day at the age of 9 years were as follows: Before breakfast, 88 systolic and 40 diastolic; at 3 p. m., in his father's office, 180 systolic and 130 diastolic; at

6 p. m., at home, 128 systolic and 60 diastolic; at 7 p. m., at home, 150 systolic and 100 diastolic, and at 8:30 a. m. on the following day, 150 systolic and 114 diastolic. The variability was as great throughout life; on one occasion, at the age of 16, it was 185 systolic and 150 diastolic; two months later, 128 systolic and 80 diastolic, and on the same afternoon, at a ball game, 152 systolic and 100 diastolic. The highest measurement was 220 systolic and 160 diastolic, less than one year before death. A day later the blood pressure was 120 systolic and 80 diastolic.

*Clinical Diagnosis.*—The clinical diagnosis was hypothalamic attacks of undetermined origin and amyotonia congenita.

*Anatomic Diagnosis.*—The anatomic changes, which will be described in detail in the accompanying article, were acute necrosis of the liver, minimal glomerulonephritis, asthmatic bronchitis and minimal acute bronchopneumonia, and "status thymicolymphaticus." In the nervous system, there was found an old lesion which had destroyed portions of the dorsomedial nucleus, the internal medullary lamina and the lateral nucleus of the right thalamus. Acute congestive changes and some perivascular hemorrhage were scattered throughout the central nervous system. The spinal cord showed changes in the anterior and lateral horns and in the posterior columns.

This boy had a nonprogressive, episodic disease, with onset in infancy. The nature of the attacks was discrete, and apparently each episode resembled the preceding one. It is stated that febrile attacks were provoked by emotional excitement. Each attack began abruptly, followed by elevation of temperature for several days, with pronounced fluctuations in temperature during this period, and, finally, by defervescence over the course of two or three days. With the onset of these attacks the patient would complain of coldness; he would shiver, and sometimes he had a chill. There was associated pallor of the face and extremities. The hands and feet were cold, the trunk warm. Sweating was absent. Piloerection was not noted. The sudden defervescence was marked by sudden, profuse sweating, warm extremities and flushing. The attacks were also associated with vomiting, nausea, diarrhea and pain in the extremities. There were formed elements, casts and albumin in the urine during the attacks, and the blood urea nitrogen level generally rose. The blood pressure fluctuated between hypertension and hypotension, but there was no consistent trend during the attack. Attacks were said to be aborted by pentobarbital, but it was also reported that the fever was reduced with antipyretic drugs. It was learned that this child had had a high temperature during attacks of measles and chickenpox. In all of the febrile attacks he was described as being extremely ill; during the period of rise in temperature he sometimes looked almost moribund.

Since the attacks of fever are important in the case, one might digress a bit to discuss heat regulation. The body temperature depends on a balance between heat dissipation and heat conservation and formation, and in the final analysis is controlled at the periphery.

Heat dissipation is mediated through the mechanisms of radiation, convection and conduction, and of evaporation of water from the surface. A body will radiate heat to neighboring structures which are at a lower temperature. Physiologically, this radiation is controlled by vasodilatation. By increasing the blood flow to the skin, a greater volume of circulating blood is brought nearer the surface, and hence there is a greater dissipation of heat. Evaporation of water from the surface leads to cooling. This is mediated chiefly through the mechanisms of sweating. A small amount of evaporation from the skin takes place without sweating, the so-called insensible water loss. In animals panting is important. These are the specific mechanisms of lowering body temperature.

Heat conservation is effected through (1) piloerection, which is not an effective means of heat conservation in human beings, and (2) peripheral vasoconstriction. In addition, the body can raise its temperature by increased heat formation; the most common mechanism by which this is done is increased muscular activity or shivering; shivering may become so marked as to constitute a chill. In addition, there may be an increase in general cellular metabolism. The latter plays an important role in the fever of infections, reaction to foreign proteins, etc.

Each of these factors may be modified by a number of things. When environmental temperature exceeds body temperature, radiation, convection and conduction can no longer be effective, and evaporation, through sweating, plays the major role. Peripheral changes which involve circulation and sweating will affect body temperature. Any morbid process or drug which causes prolonged peripheral vasoconstriction may cause the internal body temperature to rise. This was illustrated in a patient with a pheochromocytoma of the adrenal.[3] Similarly, drugs that cause increased sweating or increased peripheral circulation may lead to lowering of body temperature. It is not uncommon to see in dying patients a terminal rise in body temperature to 104 or 105 F., accompanied generally with marked pallor, vasoconstriction and

3. Engel, F. L.; Mencher, W. H., and Engel, G. L.: Epinephrine Shock as a Manifestation of Pheochromocytoma of the Adrenal Medulla, Am. J. M. Sc. **204:** 649-661, 1942.

cold hands and feet; actually, such persons are in shock. But their ability to dissipate heat is impaired because of the intense vasoconstriction, and in spite of the cold skin the rectal temperature may be high.

In studies of the central regulation of temperature, it has been well established that heat-regulating centers are located in the hypothalamus. In the anterior portion are located nuclei that have to do with heat dissipation. Stimulation of this area by galvanic current or by warming results in sweating and vasodilatation (and panting in animals). The destruction of this region in acute experiments results in hyperthemia, due to relative overactivity of the centers for heat conservation and formation, and in chronic preparations, in inability to adjust to high environmental temperature.

The centers for heat conservation and formation are located in the posterior portion of the hypothalamus, stimulation of which produces piloerection, shivering and vasoconstriction, destruction resulting in hypothermia and inability to adjust to lowered environmental temperatures. When both these hypothalamic centers are destroyed, varying degrees of poikilothermia may result.

From the clinical data on this patient, it is apparent that all means of temperature regulation were intact, but there seemed to have been some imbalance between the two functions. One is immediately struck with the similarity between the febrile attacks described here and those resulting from stimulation of the posterior hypothalamus or destruction of the anterior hypothalamus. In addition, the fact that these attacks were prevented by administration of pentobarbital focuses attention on the hypothalamus. Ranson and Clark [4] demonstrated that pentobarbital will inhibit the centers for heat formation and conservation in the posterior hypothalamus.

However, it is also known that this boy had flushing and sweating. This suggests that at first the posterior hypothalamus was stimulated, with resultant shivering, vasoconstriction and hyperthermia, and that then the anterior hypothalamus was stimulated and there resulted sweating, flushing and a fall in temperature. This alternation seemed to go on over a period of days, with rapid swings in temperature, until normal temperature was again restored. There must therefore have been some disturbance in the relationship between the two portions of the hypothalamus concerned with heat regulation.

4. Ranson, S. W., and Clark, G.: Neurogenic Fever Reduced by Nembutal, Proc. Soc. Exper. Biol. & Med. **39**:453-455, 1938.

At this point the question might be raised whether this boy had any other signs that might be ascribed to hypothalamic disturbance. Gastrointestinal symptoms such as those described as exhibited by this patient during his attacks have been demonstrated in animals on stimulation of the anterior hypothalamus.[1] The fluctuating hypertension suggests involvement of the blood pressure regulating mechanism in the posterior hypothalamus. Less certain to be of hypothalamic origin are the attacks of breath holding followed by somnolence, which in certain respects resembled narcolepsy or cataplexy. Hyperphagia has been produced in animals by hypothalamic lesions, but these animals usually become very obese.[5] This patient was almost a dwarf; we are not aware of the combination of hyperphagia and dwarfism being produced by hypothalamic lesions. Thus there are a number of symptoms which may definitely be related to the hypothalamus and others which might be.

To summarize the case thus far, we are dealing with a case of a nonprogressive, episodic disease in which our data suggest a disturbance in hypothalamic function and which was associated with a lesion in the thalamus on one side. Also, there was a generalized disturbance in the muscles, which were small and somewhat weak. The deep reflexes were lost, and there were lordosis, scoliosis, bulbar speech without evidence of bulbar palsy, drooling and defective convergence. Essentially, too, the boy was a symmetric dwarf. Smallness was not confined to the muscles, because the skeleton was also small. Osseous development, as measured by bone age, however, was normal.

Further, the boy had absence of secondary sex characteristics, no pubic hair and underdevelopment of the external genitalia. All these secondary abnormalities might be explained partially by the extreme loss in weight resulting from the repeated episodes of fever. He was said to have lost from 8 to 10 pounds with each attack. With such a handicap, it is obvious that this boy had to gain more than 100 pounds (45.4 Kg.) just to make up his periodic loss of weight, a fact which may also account for the muscular dystrophy. In short, these manifestations may have been indirect results of the central disturbance. Whether there was a more direct relation to the thalamic lesion and the hypothalamic dysfunction cannot be established from the data available.

It is clear from this analysis that in this case there was a paroxysmal disturbance in the central

5. Brobeck, J. R.; Tepperman, J., and Long, C. N. H.: Experimental Hypothalamic Hyperphagia in Albino Rat, Yale J. Biol. & Med. **15**:831-853, 1943.

regulation of body temperature, the circulatory system, the gastroenteric tract, respiration and sleep together with a more sustained derangement in somatic and secondary sexual development, which may have been at least partially secondary to the paroxysmal disturbance. This syndrome, which eventually proved fatal, was associated with a minute, fixed lesion of the right thalamus, which undoubtedly interrupted to some degree the connections of the hypothalamus with higher centers, and perhaps with lower vegetative centers.

The similarity between the symptoms experienced by this patient and the manifestations provoked in animals by stimulation of various portions of the hypothalamus admits of no argument; yet the hypothalamus in this patient was uninvolved. Indeed, had the hypothalamus been involved, one might anticipate a quite different clinical picture, characterized by a more or less fixed disturbance in vegetative function, and, in all likelihood, the boy would not have survived long after such damage had been sustained. It is of more than theoretic interest to inquire into the possible mechanisms of the attacks.

Penfield[2] referred to the attacks of hypothalamic activity experienced by a patient with an encapsulated tumor in the third ventricle pressing on the thalamus as "diencephalic autonomic epilepsy." In his patient, the attacks, which in certain respects resembled those experienced by our patient but were of much briefer duration and of more explosive character, could be adequately explained by variations in the degree of pressure by the tumor on the thalamus. In this sense the tumor could be regarded as a local source of irritation which provoked a discharge, either by involvement of a higher neural pathway or by direct involvement of the hypothalamus. The concept implicit in the term "epilepsy" appears valid in such an instance.

In our case no such mechanical factor can be invoked. One might consider the lesion analogous to a cortical cicatrix secondary to craniocerebral injury, and as such an epileptogenic focus. The hypothalamus, however, is not analogous to the cortex. As the main center for the mediation of autonomic function, it is under the constant influence of both excitatory and inhibitory impulses from higher centers and of afferent impulses from the periphery. The lesion in the thalamus acted to interrupt to some degree the higher cortical control of hypothalamic function. This could lead to overreaction of this region to the continuous inflow of afferent impulses, a release phenomenon in the sense defined by Hughlings Jackson. Analysis of the provocative factors of the various attacks tends to confirm this interpretation. Stimuli that normally lead to febrile responses, such as intercurrent infections, in this boy led to excessive rises in temperature. Some emotional experiences which ordinarily are expressed through various changes of a vegetative nature, provoked caricatures of such reactions. The attacks were not "spontaneous," but were all tripped off, sometimes by situations obviously charged with anxiety, sometimes by more subtle provocation. The dynamics involved in this case can thus be fully clarified only by a more detailed analysis of some of the psychodynamic factors.

## PSYCHIATRIC DATA

No detailed psychiatric evaluation in this case was made during life. The following rather fragmentary observations were reconstructed in retrospect.

The patient was born four to five weeks prematurely, the younger of 2 sons of a pediatrician. The first born was 4 years older than the patient and was normal in all respects except for a labile blood pressure, from which the mother also suffered. The father was energetic and ambitious and stuttered somewhat. From birth the child was considered abnormal; early he presented a difficult feeding problem. Later the underdevelopment and dwarfism, the asthma, the difficulty in muscular coordination and the bizarre attacks all served to set him apart from his older brother and from other children. The anxiety of the parents was understandable and was indicated by the weight of medical attention with which the child had to cope, practically since birth—only a little of it is detailed in the medical history.

Despite these intellectual, physical and psychologic handicaps, the boy tried to compete with normal children. He trained in regular school, was taken into a boy scout troop, played in piano recitals and took part in other competitions. There is every indication that he felt a strong need to demonstrate his ability and to deny his disabilities. It is usual to find that the prolongedly ill child either remains infantile or acquires an attitude of complete denial of the illness. The latter, rather, was the case with this boy; yet, at the same time, he was repetitively faced with new and confusing medical examinations, which served greatly to entrench his feelings of insecurity and to expose to him the family's underlying anxiety. As has any child with a chronic disability, he had a greater need for love and reassurance. Actually, he repeatedly participated in group activities, where he had difficulty in holding his own. Frustration and conflict are easily understandable in such circumstances. Rage and resentment were not expressed verbally. The child was extremely obedient and amenable to any suggestion or request. It is noteworthy that the episodes of breath holding usually occurred in circumstances in which anger was likely.

Comments by two of the psychologists who were asked to estimate the intellectual attainment of this boy are of some interest. When the patient was 5 years old, one noted: "The examiner is inclined to believe that

the boy could do better if he had more confidence in himself. A pitiful, faint whisper, 'I don't know,' was generally his first reply. . . . He will certainly profit more by being taught at home, and where he is allowed to express his own ideas, than he will in a large group of children. He needs constant encouragement, but also the companionship of other children." When the patient was 13, another examiner noted: "An interesting sidelight occurred in the free association test for the age of 10 years. The word 'school' was followed by 'unhappy,' and later the word 'happy' brought forth 'baseball,' 'field' and 'game.'" These comments reveal the child's deep-seated insecurity, as well as some of the conflicts he experienced with respect to school and play. While these responses would not be uncommon among normal children of this age group, in this child they tend to confirm the impression of rebellion against the level at which he was expected to compete, a level which served as a denial of his disability.

Some of the situations which appeared to precipitate attacks are of interest. Contemplation of an impending examination in school was probably the most frequent offender, although the episodes also occurred after the excitement of attending a football game, preceding a trip or before coming home after a period away from it. These are circumstances that might be expected to provoke excitement, and even anxiety, in normal children. That they had an even greater impact on this boy and that his defenses were less adequate is highly probable.

In retrospect, it would be hard to imagine how his psychologic development could have been more battered by the medical handling he received. He was treated in a manner which would mobilize anxiety, but he had little means of handling it. His immediate environment demanded that he display none of it. In addition, he had a deficit in certain nervous structures which further impaired his ability to allay anxiety. At no time during his long contact with medical aid did the problem of his emotional adjustment to his disability appear to receive much thought.

The relation of the feverish attacks to what were for this boy strenuous and intolerable situations was repeatedly demonstrated to the satisfaction of those who had the most to do with him. Psychogenic factors certainly initiated many of the attacks, the final of which resulted in death.

The patient had a lesion of the right thalamus which apparently partially interrupted corticohypothalamic connections. It is well established that the hypothalamus is the main way station for the autonomic reactions that accompany the expression of emotions. These autonomic reactions normally serve the useful purposes of preparing the organism for the activities required for fighting, fleeing, acquisition of food, mating, and the like, and, as goal-directed activities, are under higher cortical control.[1a] In this patient, it may be postulated that this higher cortical control was incomplete because of the interruption of neural pathways.

The patient was subjected to considerable environmental stress of an anxiety-provoking character. This sick lad produced a blow to his family's self esteem, to which the latter never adjusted. The patient's early anxieties were the result of family anxieties and were of such magnitude that one would expect a structurally normal child in comparable circumstances also to manifest neurotic reactions. Unquestionably, the child felt rejected since he could not come up to family standards. Because of family attitudes, he felt an overwhelming need to act and behave as a normal child. The ordinary dependent and infantile longings of any child for security were repressed in him.

The boy found himself in one situation after another which provoked anxiety in him (school, scouting, competitions), but, because of the interruption of the corticohypothalamic pathways, the autonomic manifestations of the anxiety went far beyond normal expression, both qualitatively and quantitatively, and resulted in the clinical picture and finally in death. Why distortions of some hypothalamic activities (notably temperature regulation) were more prominent than others is not clear, but the marked tendency to overshoot in either direction is consistent with the absence of normal moderating influences. In other words, because of the structural lesion, the response was poorly directed, excessive and uneconomical, tended to be self perpetuating and was essentially destructive, rather than protective, to the patient. This was true whether the reaction was initiated by psychologic factors (anxiety), physiologic factors (intercurrent infection) or a combination of the two.

Clearly, proper therapy should have been directed toward protecting the patient from anxiety-producing situations until he might have developed better defenses to handle his disability. Denial was not an effective means of doing this. It is worth pointing out that experimental animals with chronic hypothalamic lesions may get along well if not put under environmental stress.

Obviously, this explosive type of autonomic reaction in response to psychogenic or physiogenic stimuli is not confined to patients with lesions of the central nervous system involving hypothalamic connections. A comparable example of an explosive sympathetic discharge provoked by similar factors may be cited[3] in a patient with an epinephrine-secreting tumor of the adrenal medulla (pheochromocytoma). Indeed, comparable mechanisms for the production of "attacks" in many diseases (e. g., epilepsy, migraine, cardiac disorders) in the presence of a great variety of structural lesions involving many different organ systems could be cited.

This case demonstrates the importance of a liberal and dynamic approach to the interpretation of symptoms. The demonstration of the lesion in the thalamus provided a starting point, but nothing more, for an understanding of symptom formation in this patient.

## SUMMARY

An 18 year old boy had recurrent attacks of coryza, chills, fever, nausea, vomiting, abdominal cramps, oliguria, fluctuating hypertension, tachycardia and muscle cramps, beginning at the age of 5 months. The patient eventually died during such an attack. The attacks developed during anxiety-provoking situations or in the course of intercurrent infections. The patient also had frequent episodes of breath holding, cyanosis and unconsciousness, followed by somnolence, which began on the third day of life. He also had bronchial asthma and pronounced skeletal, muscular and genital underdevelopment.

Postmortem examination revealed a small cystic softening involving portions of the dorsomedial nucleus, the internal medullary lamina and the lateral nucleus of the right thalamus. The hypothalamus was intact.

The lesion interrupted partially corticohypothalamic connections and led to distortion and exaggeration of hypothalamic reaction in response to physiogenic and psychogenic stimuli. An analysis of psychodynamic factors revealed the importance of anxiety in provoking poorly moderated and directed hypothalamic responses.

Cincinnati General Hospital (29).

# HYPOTHALAMIC ATTACKS WITH THALAMIC LESION

## II. ANATOMIC CONSIDERATIONS

CHARLES D. ARING, M.D.
AND
GEORGE L. ENGEL, M.D.
CINCINNATI

An extensive neuropathologic study was undertaken on a young man aged 17¾, who died in one of an extended series of attacks of hyperthermia. He had been studied rather exhaustively clinically, having been examined by more than one hundred physicians; it was recognized during the latter part of his life that the attacks from which he suffered were most likely due to disturbed hypothalamic function.

Since the study appeared to cast some light on thalamic and hypothalamic function, and more on hypothalamic regulation, it was deemed advisable to record the neurohistologic findings in some detail. The clinical data and the physiologic and psychosomatic aspects were discussed in the foregoing article.[1]

### PATHOLOGIC REPORT

*Postmortem Examination.*—The examination was performed two hours after death. The body was that of a small, somewhat poorly nourished white male whose size and conformation suggested an age not over 12 or 14 years. The hair was sparse except on the head and was normally distributed.

The genitalia were immature; the testes and epididymides were distinctly smaller than normal. The prostate gland was infantile in size and was compressed and scarcely recognizable. The adrenal glands were somewhat smaller than average. The thymus was distinctly large, measuring 10 cm. in length and varying in width from 1 to 3 cm. and in thickness from 0.5 to 1.5 cm. The spleen was moderately enlarged.

All extremities were of proportionate size and development. There were some clubbing of the finger tips and reddening of the distal phalanges. The muscular tissue everywhere appeared grossly diminished in amount; there was no focal muscular atrophy.

*Microscopic Examination of the Viscera.*—Exclusive of changes in the nervous system, the micropathologic findings consisted of a moderate degree of focal acute pneumonitis, chiefly peribronchial in distribution. There was marked thickening of the bronchial walls due to proliferation of connective tissue and infiltration with lymphocytes and eosinophils. The basement membrane was thick and hyalinized, beneath an intact bronchial mucosa. The latter changes were considered to be consistent with those of an allergic form of bronchitis.

In the liver numerous scattered areas of focal necrosis were found, chiefly in the central zones, and they were associated with infiltration of polymorphonuclear leukocytes. The tissue necrosis was an acute reaction, without evidence of scarring or repair. In the severe lesions only phantoms of liver cells remained. The liver tissue which remained intact presented acute passive congestion. There was no abscess formation or retention of bile.

There was moderate congestion of the kidneys. Occasional small areas of scarring involved the tubular and interstitial tissue, and an occasional glomerulus was reduced to a fibrous ball. Sometimes concentric scarring was seen around Bowman's capsule.

The adrenal glands were microscopically normal except for vascular engorgement.

Some hyperplastic reticulum was seen toward the central portion of the thymic lobules. Structures suggestive of Hassall corpuscles, with degenerative changes, were noted. There was pronounced congestion of the thymus gland.

Sections of hilar, aortic and mesenteric lymph nodes contained greatly dilated sinusoids and hyperplastic reticulum and endothelium. Remnants of follicles were seen; there were old and recent degenerative changes. There were scattered chromatin flecks, necrosis of cells and, in places, cellular infiltration. The older change was indicated by hyalinization and scarring. Congestion was marked throughout.

In the spleen the majority of malpighian bodies showed central degenerative changes, principally hyalinization and scarring. Superimposed on the chronic change were acute alterations, consisting of chromatin flecking and vascular engorgement.

Sections from the gastrocnemius muscle revealed no abnormality. The pituitary gland was normal.

*Macroscopic Examination of the Central Nervous System.*—All the surfaces of the brain were congested. The development of the cortex appeared normal. The blood vessels of the circle of Willis were of normal distribution and did not show structural change.

Vertical sections of the brain were made at 6 mm. intervals. Congestion of all vessels was noted. A small cystic cavity within the dorsomedial and lateral nuclei of the right thalamus was found (fig. 1), which measured 9 by 1.5 by 2 mm. The long axis of the cavity was on the oblique plane of a projected line drawn from the inferior aspect of the third frontal convolution (dorsally) to the ventralmost aspect of the third ventricle (ventrally), where it extended to within 3 mm. of the ependymal lining of the third ventricle (fig. 1). Dorsally it reached to within 5 mm. of the border between

From the Departments of Internal Medicine (Neurology) and Psychiatry, University of Cincinnati College of Medicine, and the Laboratory of Neuropathology, Cincinnati General Hospital.

1. Engel, G. L., and Aring, C. D.: Hypothalamic Attacks with Thalamic Lesion: I. Physiologic and Psychologic Considerations, Arch. Neurol. & Psychiat., this issue, p. 37.

the external capsule and the lateral aspect of the lateral thalamic nucleus. The nerve tissue immediately adjacent to the cavity appeared homogeneous and was slightly firm to touch.

The remaining portions of the central nervous system showed no gross abnormalities.

*Microscopic Examination of the Central Nervous System.*—Sections from many cortical areas, from the thalamus on both sides, from the hypothalamic region, from the cerebellum, from six levels of the pons and medulla and from eight levels of the spinal cord (first, fourth and eighth cervical; second, fourth and eighth dorsal, and first and fifth lumbar) were stained with hematoxylin and eosin, cresyl violet and the Loyez, Bodian 1 per cent strong protein silver and silver carbonate methods. From the pituitary gland, sections including the anterior and posterior lobes and the intermediate area were stained by the Biggart technic.

were slightly but definitely larger than those on the right (fig. 1). On the right the lateral portion of the dorsomedial nucleus and a small bit of the mesial portion of the lateral nucleus of the thalamus were destroyed by a cyst which has already been described. The cyst cavity extended across the midportion of the internal medullary lamina and roughly was estimated to destroy about 5 per cent of the lateral nucleus and about 50 per cent of the dorsomedial nucleus of the right thalamus. In serial sections of the thalamic nuclei the cyst occupied a more dorsomedial portion the more posteriorly one examined, though it nowhere communicated with the third ventricle.

Demyelination of the fibers of the right dorsomedial nucleus was massive and extended to the periependymal fibers running from this nucleus to the hypothalamus. Other periependymal fibers running to the stria medullaris and the habenular ganglion were involved. The

Fig. 1.—Vertical section through the dorsomedial nuclei of the thalamus. Note the cyst which has destroyed the cellularity of the ventral half of the right dorsomedial nucleus and which traverses the internal medullary lamina to involve slightly the lateral nucleus. Congestion is also shown. Loyez stain; × 5.

There were marked congestion of all vessels throughout the central nervous system and scattered areas of diapedesis, more numerous in the brain stem. On one side of the medulla, at the midolivary level, clusters of punctate hemorrhages were located in the dorsal motor nucleus of the vagus nerve. In sections stained with cresyl violet it was possible to determine that these hemorrhages had existed long enough to cause destruction of about one-half the cells of this strategic nucleus; some of the remaining cells were shrunken in appearance. There had also been a perivascular extravasation of similar type in the descending autonomic bundle (the dorsal longitudinal fasciculus of Schütz). The cerebrum and cerebellum were normal except for the acute changes associated with severe congestion.

The left thalamus showed no abnormality except for vascular engorgement. The thalamic nuclei on the left

fibers from the right medial nucleus of the thalamus to the association areas of the frontal lobe, i. e., those comprising the right anterior thalamic radiation, were demyelinated. The medullary striae, the centrum medianum and the subthalamic structures were normal bilaterally.

The inner surface of the cystic cavity was sharply outlined by a thin membrane formed by glial nuclei and strands of glial fibers, loosely adherent to the inner wall of the cavity (fig. 2), which contained a few congested, small blood vessels. No gitter cells or signs of inflammation were present.

The tissue immediately surrounding the cyst showed marked disorganization, where the large majority of nerve cells were destroyed. Those remaining showed far advanced degeneration: they had undergone almost complete calcification (fig. 2).

The affected nerve cells could be identified only by their shape and size. They stained a deep, rather uniform black in silver preparations, which delineated them as irregularly nodular (figs. 2 and 3). The nodularity extended throughout the body and processes of the cells to such distances as the processes had taken the stain. It appeared as though neurofibrillary material had swollen, fragmented and filled the cell. The neuronal change, clearly defined in the silver stains only, became less obvious as one examined progressively away from the cyst, and could be barely identified in the cell stains, where the cells appeared shadowy and vacuolated. Nuclei or nucleoli could not be discerned in any of the involved cells.

In addition to calcified thalamic nerve cells, the abnormal tissue was composed of large masses of irregularly arranged glial cells. There were some mature astrocytes recognizable. The wall of the third ventricle immediately adjacent to the cyst was lined by ependymal cells, beneath which several layers of bipolar spongioblasts were arranged parallel to the ventricular wall. No nerve cells or myelinated fibers could be found in the paraventricular region mesial to the cyst. Axis-cylinder preparations of this area revealed the almost complete absence of nerve fibers. The dorsal half of the dorsomedial thalamic nucleus showed no change, and the other thalamic nuclei, except the mesial bit of the lateral nucleus, appeared normal.

All of the hypothalamic nuclei were examined carefully and were normal. The structures of the mesencephalon, the inferior and superior colliculi and the tegmentum were normal. The brachium conjunctivum contained a normal complement of fibers. The red nuclei as well as the nuclei of the cranial nerves were normally developed, and the nerve cells were well preserved except for the acute change noted in the vagus nucleus on one side. The aqueduct of Sylvius and the adjacent gray substance disclosed no pathologic change.

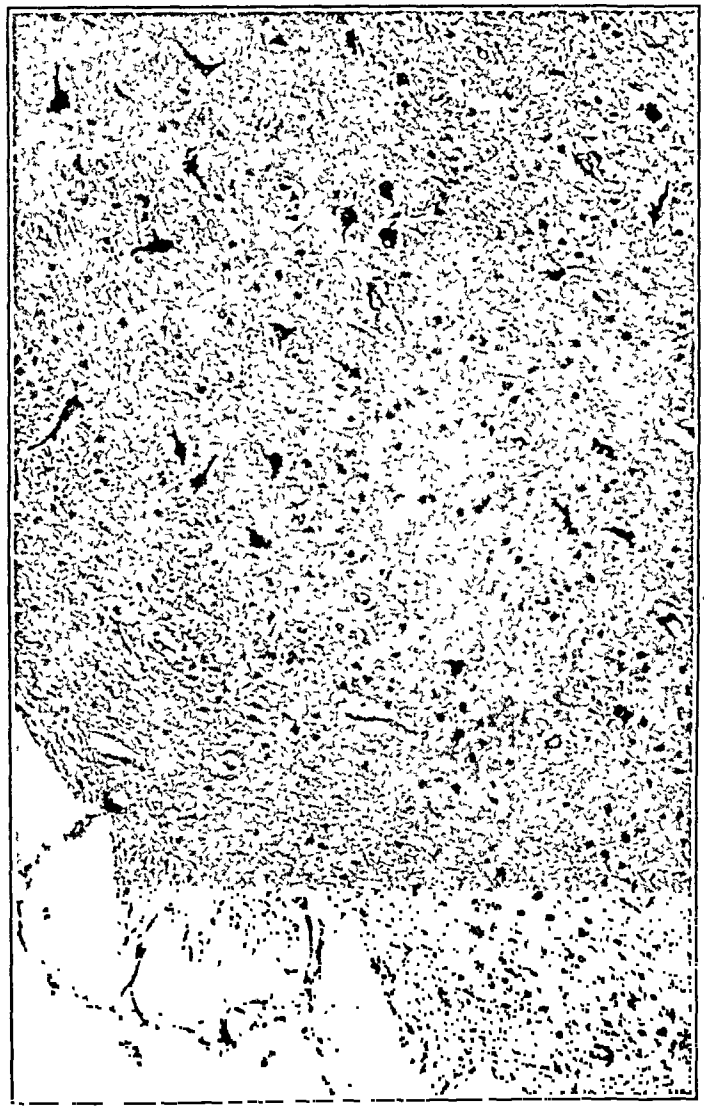


Fig. 2.—A portion of the right dorsomedial nucleus of the thalamus, bordering on the cyst. Note the loosely adherent membrane lining the cavity of the cyst and the loss of nerve cells and fibers. The nerve cells remaining are calcified. Bodian stain; × 160.

All of the cerebellar peduncles were normal. Within the lateral portion of the reticular formation on one side of the pons and medulla, there was a slight but definite decrease in nerve fibers and myelin sheaths, as compared with the same structures on the opposite side. This destruction was probably of a descending bundle of fibers which stream out of the posterior hypothalamus and which are probably primarily orthosympathetic. They take up a fairly diffuse position in the reticular formation.

In the cervical and upper thoracic segments of the spinal cord there has occurred almost complete destruction of the nerve cells of the lateral horn on one side. The few remaining cells disclosed marked degenerative

changes with neuronophagia. The sympathetic cells of the opposite side were in a moderately good state of preservation.

Myelin sheath preparations revealed that in the first cervical segment of the spinal cord, in the concavity between the dorsal horn and the lateral projection of gray substance (lateral fasciculus proprius) on one side, there was a circumscribed area of demyelination (fig. 4) implicating a small number of longitudinally running fibers which were intimately interlaced with the gray substance. Some of these myelin sheaths were broken into globules. The nerve cells in the lateral gray substance were destroyed on the same side.

segments of the spinal cord. In some areas there was complete lack of large anterior horn cells. The remaining cells disclosed satellitosis and neuronophagia. There was a slight increase of small glial cells. All changes were more pronounced in the anterior horns on the same side as the damage to the lateral horn.

In the lower thoracic, lumbar and sacral segments the nerve cells were in a moderately good state of preservation, though possibly slightly reduced in number.

There was moderate loss of myelin in the posterior columns of the spinal cord throughout its length, more marked in the fasciculus cuneatus than in the fasciculus gracilis. The loss of myelin sheaths was most obvious

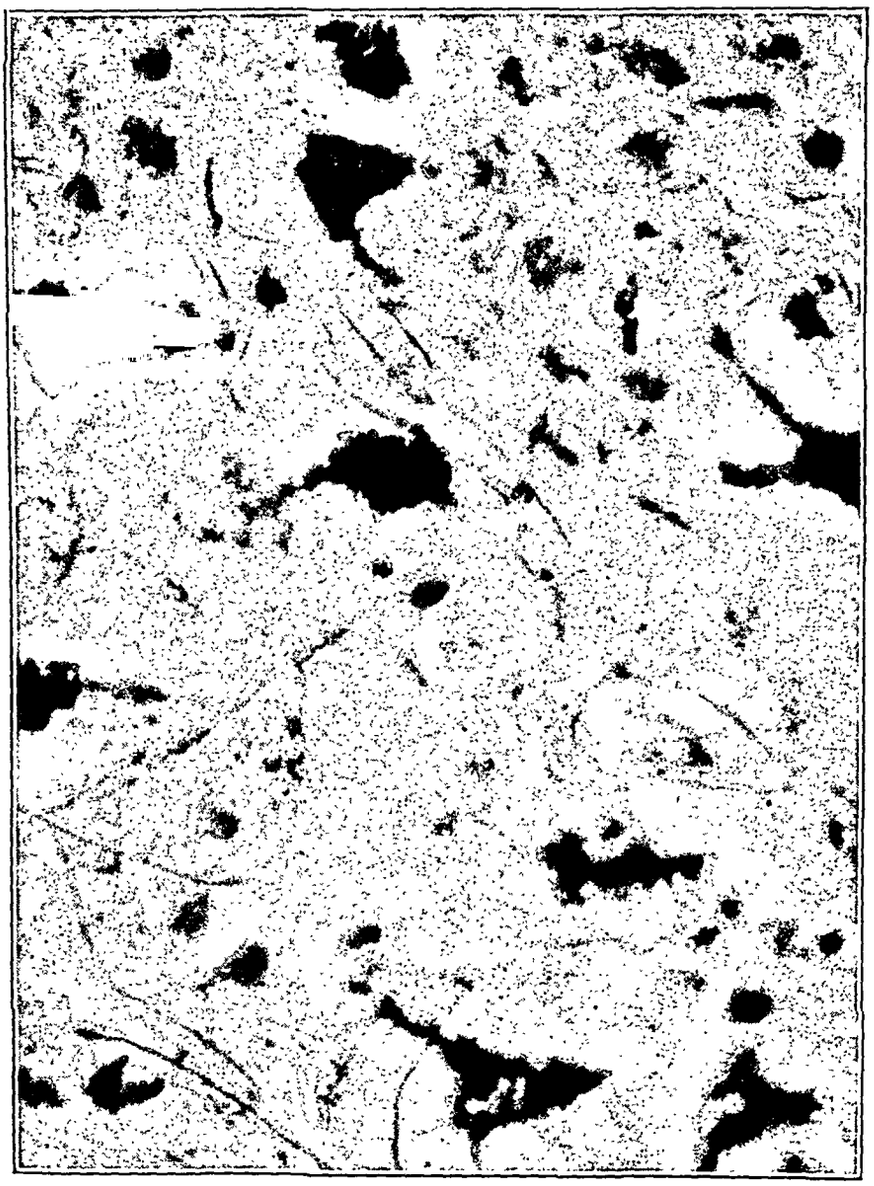


Fig. 3.—Section showing the detail of the calcified nerve cells in the right dorsomedial nucleus of the thalamus and the paucity of nerve fibers. Bodian stain; × 1,000.

This region, which appeared pale in myelin sheath preparations, showed a reduction of nerve fibers (fig. 5) in the sections impregnated with silver according to the Bodian method. Some of the remaining axons were either irregularly swollen or considerably reduced in size.[2] Comparable areas in the gray and white matter on the opposite side of the cervical segments of the spinal cord were normal. The anterior horn cells were reduced in number throughout the cervical and upper dorsal immediately adjacent to the gray matter of the posterior horns and the gray commissure. The spinal roots were normal until they entered the spinal cord, at which point it seemed that some degeneration had occurred.

In summary of the pathologic changes in the nervous system, there was found an old lesion which destroyed the ventral half of the dorsomedial nucleus and a bit of the internal medullary lamina and of the lateral nucleus of the thalamus on the right. There was rarefaction in the reticular substance of one side as it traversed the regions of the pons, medulla and upper cervical segments of the cord. The cells

2. Dr. A. M. Lassek, professor of anatomy, Medical College of the State of South Carolina, when shown these sections, noted the destruction of cells of the lateral substance and nearby tracts on one side. He noted the close relation of the fibers in question to the pyramidal tract and said there was no known tract in this vicinity.

in the lateral gray matter and the lateral horns on one side of the cervical and upper thoracic segments of the spinal cord were destroyed. The anterior horn cells of the spinal cord were affected, especially those of the rostral portion of the cord. There was some demyelination of the white matter of the posterior columns of the spinal cord. Acute congestive changes were seen throughout the central nervous system.

Fig. 4.—Discrete demyelination in the lateral fasciculus proprius of one side of the first cervical segment of the spinal cord. (To the left is gray matter; to the right, white matter). Loyez stain; × 160.

Findings outside the nervous system included acute necrosis of the liver, minimal glomerulonephritis, asthmatic bronchitis and minimal acute bronchopneumonia and the condition which has been termed by some "status thymolymphaticus."

## COMMENT ON CLINICOANATOMIC FEATURES

The unilateral deterioration of long tracts in the reticular substance of the pons, medulla and upper cervical segments of the cord, associated with destruction of cells in the lateral gray matter and in the lateral horns of the cervical and upper thoracic segments of the spinal cord, deserves a word. The inference is that a system of fibers and cells was affected in a long-standing degenerative process and that the localities involved are those harboring structures subserving autonomic function.

Magoun [3] has described a pathway in the brain stem of cats which descends either directly or through relays to preganglionic sympathetic neurons in the spinal cord. This pathway arises from the lateral hypothalamic area, and in the medulla it is distributed chiefly in the lateral portion of the reticular formation; thence it

3. Magoun, H. W.: Descending Connections from the Hypothalamus, A. Research Nerv. & Ment. Dis., Proc. **20**:270-285, 1939.

descends in the anterolateral funiculus of the upper cervical portion of the cord. List and Peet [4] concluded that in man descending hypothalamic paths were located in analogous areas.

What the lesions of the brain stem and cord had to do in this case with the labile control of temperature and blood pressure and the periodically abnormal respiratory function, gastroenteric mobility, urinary output and content and unilateral sweating on the forehead cannot be stated. One might consider that imbalance in the innervation of structures concerned with these functions might have been brought about more readily in the presence of a disorder of the central nervous system such as this.

It is of extreme importance that a unilateral lesion in the thalamus may be associated with hypothalamic attacks. In this case, the hypothalamus was structurally normal; yet emotional factors, as well as infectious disease, provoked its functional disturbance. It seems clear that, through the interruption of certain higher pathways, it is possible to disturb hypothalamic function. In other words, the hypothalamus may be released, in the sense that Hughlings Jackson was the first to enunciate.

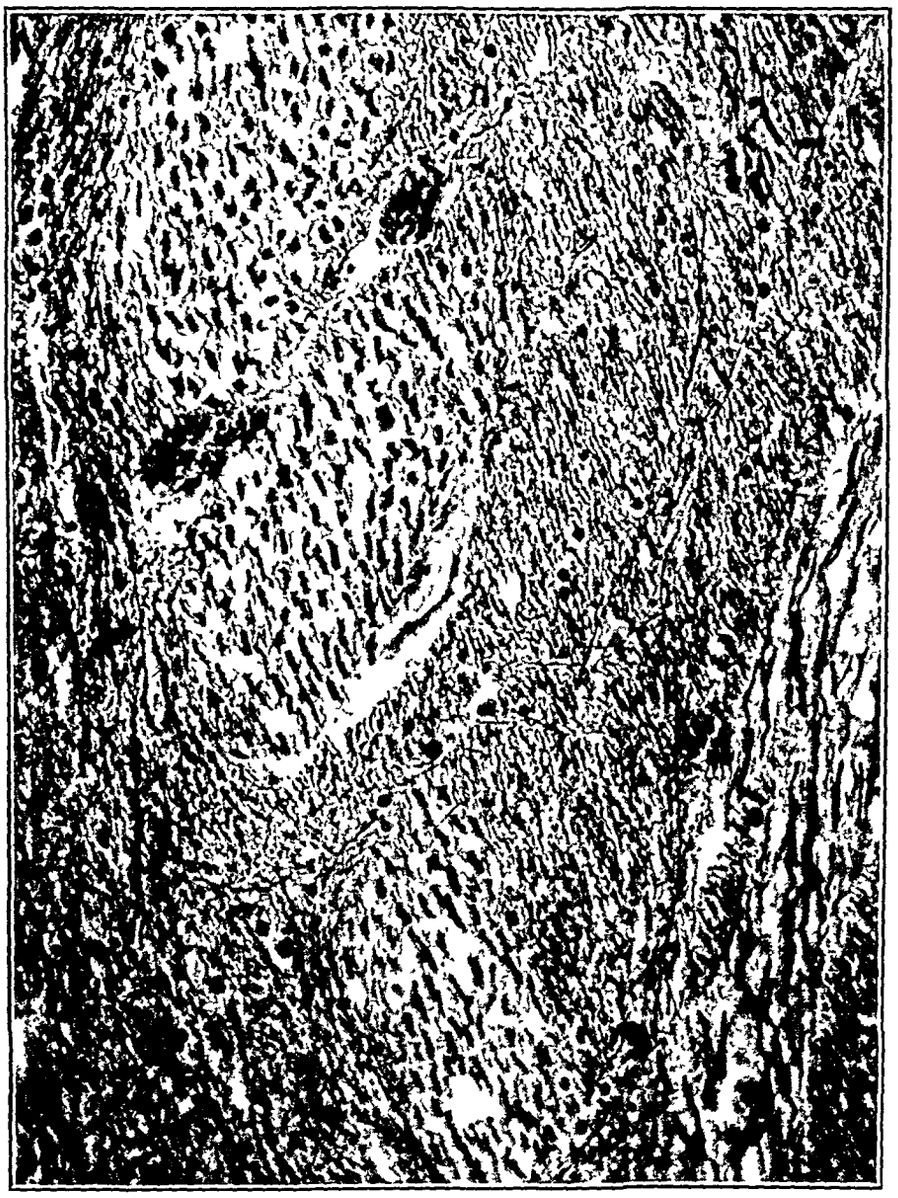


Fig. 5—Swelling and reduction of axons in the lateral fasciculus proprius of one side of the first cervical segment of the spinal cord, from a section contiguous to that shown in figure 4. Bodian stain; × 160.

If there were doubt that the hypothalamus was at fault during the attacks suffered by this boy, it should be noted that some hyperthermic episodes could be aborted with pentobarbital. As Ranson and Clark [5] have so clearly shown, a site of action of this barbiturate in man or animal may be the hypothalamus, with the resultant prevention of hyperthermia after surgical manipulations in this region.

4. List, C. F., and Peet, M. M.: Sweat Secretion in Man: V. Disturbances of Sweat Secretion with Lesions of the Pons, Medulla, and Cervical Portion of Cord, Arch. Neurol. & Psychiat. **42**:1098-1127 (Dec.) 1939.

5. Ranson, S. W., and Clark, G.: Neurogenic Fever Reduced by Nembutal, Proc. Soc. Exper. Biol. & Med. **39**:453-455, 1938.

What is known about relays between the cerebral cortex and the diencephalon? The association nuclei of the thalamus that have numerous connections with other diencephalic nuclei and project to association areas of the cerebral cortex (parietal and prefrontal) are the dorsomedial and lateral nuclei and the pulvinar. The functions of these associations possibly are inferable from their anatomic connections, and therefore the dorsomedial and lateral thalamic nuclei are thought to be concerned in some fashion in corticohypothalamic association.

At this point it may be worth recalling that pathologic studies [6] of brains that had undergone prefrontal lobotomy revealed trivial cortical damage, but the dorsomedial nucleus of the thalamus suffered severe retrograde changes, characterized by the loss of most of its cells. Further, these studies by Freeman and Watts indicate that the pathway interrupted by lobotomy is predominantly thalamofrontal, rather than frontothalamic.

An analysis of this case lends evidence that the dorsomedial thalamic nucleus transmits fibers which aid in the control of nervous function at lower levels. Possibly the clinical syndrome would not have been so readily provoked if something had not been the matter with nervous mechanisms in the brain stem and the spinal cord. The latter lesions may require consideration in any thinking about hypothalamic release by a lesion rostral to the hypothalamus, and unilateral only.

## SUMMARY

The histopathologic study of a 17¾ year old boy who was for years subject to attacks of hypothalamic dysfunction revealed an old lesion which destroyed the ventral half of the right dorsomedial nucleus of the thalamus. It is thought that analysis of this case lends evidence that this thalamic nucleus transmits cortico-hypothalamic connections. In the face of a usually symptomless but fixed thalamic lesion, normal hypothalamic regulation was rather easily disturbed by emotional factors or by infections.

6. Freeman, W., and Watts, J. W.: Physiological Psychology, in Luck, J. M.: Annual Review of Physiology, Stanford University, Calif., Annual Reviews, Inc., 1944, vol. 6, pp. 517-542.

# THYROID FUNCTION OF MANIC-DEPRESSIVE PATIENTS EVALUATED BY DETERMINATIONS OF THE SERUM IODINE

EVELYN B. MAN, PH.D., AND EUGEN KAHN, M.D.
NEW HAVEN, CONN.

Previous investigators have endeavored to discover any relation between manic or depressive states and function of the thyroid gland by determination of the basal metabolic rates of patients with such conditions.[1] It is impossible to obtain reliable and accurate basal metabolic rates for overactive or apprehensive patients. For patients without psychosis, the concentration of iodine in the serum has proved to be an extremely accurate criterion of thyroid activity. In a study of several hundred subjects with and without thyroid disease, values for serum iodine below 3 micrograms per hundred cubic centimeters indicated hypofunction,[2] and values above 9 micrograms per hundred cubic centimeters denoted overactivity of the thyroid gland. Conversely, serum iodine concentrations within the limits of 3 and 8 micrograms per hundred cubic centimeters were almost never observed for subjects with definite abnormality of thyroid function. Values between 8 and 9 micrograms per hundred cubic centimeters were obtained both for patients with hyperthyroidism and for normal subjects. There is good reason to believe that the precipitable iodine in the serum is closely related to, if not identical with, the concentration of iodine in the circulating thyroid hormone. In those patients to whom no inorganic iodine has been given, the precipitable iodine of the serum is usually between zero and 1 microgram per hundred cubic centimeters lower than the total iodine of the serum. Determination of the serum iodine has proved to be a more reliable test in the diagnosis of myxedema than the evaluation either of the basal metabolic rate or of the cholesterol concentration of the serum.[3] In cases of hyperthyroidism the serum cholesterol concentration is of little diagnostic aid[4]; the basal metabolic rate is of more value, but in doubtful cases the serum iodine concentration has proved the most reliable guide.[2]

In the present investigation, thyroid activity as measured by serum iodine determinations has been evaluated in 26 manic-depressive and in 17 depressed patients who were not typical manic-depressive persons. Nine of the manic-depressive patients were in a manic state. Eight of the non-manic-depressive patients were seen in agitated depressions.

## SUBJECTS

The histories of all 43 patients were carefully reviewed, and only the patients who were clearly manic-depressive were included in the first group. These patients were considered manic-depressive because there occurred definite ups and downs (periodicity) in their life courses. In addition, at the time of unmistakable breakdowns they manifested the classic triads of manic-depressive disturbances, which are sadness and retardation of motor activity and thought, or euphoria with hyperactivity and flight of ideas. Our notion of the manic-depressive personality implies that the person is born and dies with such a manic-depressive trend even though he never has what is called a psychosis.

These subjects have been patients during the past five years. No attempt was made to determine the serum iodine concentration for every patient with a manic or a depressed condition. The patients whose serum iodine concentrations were determined were persons who were suspected of having an abnormality of the thyroid and who clinically showed one or more of the following symptoms: palpable thyroid; questionable exophthalmos, tachycardia or tremor; abnormal obesity; thick skin or puffy eyes; thin, coarse hair, and a facial expression suggestive of myxedema. Thus, of 250 to 300 patients with a manic-depressive or otherwise depressive disorder admitted during these five years, determinations of the serum iodine of only 43 are included in this study. It is scarcely necessary to say that in the whole group the

From the Department of Psychiatry, Yale University School of Medicine.

This work was aided in part by grants from the Fluid Research Funds, Yale University School of Medicine.

1. Bowman, K. M., and Grabfield, G. P.: Basal Metabolism in Mental Disease, Arch. Neurol. & Psychiat. **9**:358 (March) 1923. Gibbs, C. E., and Lemcke, D.: Study in Basal Metabolism in Dementia Praecox and Manic-Depressive Psychoses, Arch. Int. Med. **31**:102 (Jan.) 1923. Farr, C. B.: Results of Basal Metabolism Tests in One Hundred Mental Cases, Arch. Neurol. & Psychiat. **12**:518 (Nov.) 1924; Basal Metabolism in the Psychoses, A. Research Nerv. & Ment. Dis., Proc. **11**: 221, 1931.

2. Winkler, A. W., and Man, E. B.: Serum Iodines in Subjects Without Definite Clinical Evidence of Thyroid Disease and in Those With Simple Goiter, to be published.

3. Riggs, D. S.; Man, E. B., and Winkler, A. W.: Serum Iodine in Myxedema Before and During Thyroid Medication, J. Clin. Investigation, to be published.

4. Man, E. B.: Gildea, E. F., and Peters, J. P.: Serum Lipoids and Proteins in Hyperthyroidism, J. Clin. Investigation **19**:43, 1940.

incidence of clinical signs suggesting thyroid dysfunction must have been relatively lower.

The ages of the subjects ranged from 21 to 63 years. Eight were men and 35 women. Three patients whose cases will be presented in detail (figs. 2, 3 and 4) were believed to have had true hyperthyroidism and had thyroidectomies during observation on our service. Of the remaining 40 patients, 8 had a palpable or somewhat enlarged thyroid; 6 had slight exophthalmos, and 7 had had a previous thyroidectomy.

Of the 3 patients who presented the clinical picture of hyperthyroidism, the first 2 (figs. 2 and 3) were manic-depressive patients in a hypomanic phase, and the third (fig. 4), who was not a typical manic-depressive patient, had a depression with agitation. The diagnosis of hyperthyroidism was confirmed by the pathologic reports on 2 of these subjects (cases 1 and 2). The third patient was given strong solution of iodine U. S. P. for two months prior to thyroidectomy. No hyperplasia was observed in the excised gland, which showed complete involution, with adenomatous masses, some of which had apparently degenerated. Considering the duration of iodine therapy, the pathologic observations did not refute, but could not confirm, the clinical diagnosis of hyperthyroidism.

Serum iodines, either total or precipitable, were determined by the Riggs and Man potassium permanganate acid ashing method,[5] with modifications published later.[6]

All iodine determinations were made on precipitated serums when patients were under iodine therapy. At other times, the serum iodine was determined as total iodine in some cases and as precipitable iodine in others. In these instances no differentiation has been made between total and precipitable iodines because the amount of inorganic iodine in serum is minute unless iodine therapy or contamination has occurred. Serum cholesterols were determined by a gravimetric digitonin procedure.[7] Blood was drawn without stasis from the antecubital vein when the patient was in the postabsorptive state before breakfast. Basal metabolic rates were determined with Collins' Benedict-Roth or Sanborn's motorgraphic modification of the Benedict apparatus.

## RESULTS

In figure 1 the distribution of iodine values for the 43 patients is shown. Only one value is given for each patient. When more than one determination of serum iodine was made, an average value was used, except that only the initial values are presented for the 3 patients who had thyroidectomies on our service. With the omission of these 3, 36 of the 40 patients had serum iodine values within the normal range of 3 to 8 micrograms per hundred cubic centimeters. In view of the limited number of studies, the general incidence of the values for the 36 patients follows the trend of a normal distribution curve. The iodine values for 27 of the 36 patients fell within 4.5 and 6.5 micrograms per hundred cubic centimeters, the middle of the normal range.

Values for the serum iodine of 22 of the 26 manic-depressive patients fell within the normal range of 3 to 8 micrograms per hundred cubic centimeters. The iodine values for the other 4 subjects were all above 8 micrograms per hundred cubic centimeters. Two of the subjects had outspoken clinical hyperthyroidism and were treated by subtotal thyroidectomy. The serum iodine concentration for a third subject was 8.1 micrograms per hundred cubic centimeters, a borderline value which does not exceed the normal range by the experimental error of the method. The fourth patient, with a serum iodine level above 8 micrograms per hundred cubic centimeters, was a depressed, 49 year old man. About four months before his admission to the New Haven Hospital, he had been suspected of hyperthyroidism and had been given strong solution of iodine U.S.P. for a couple of months. At the time of his admission there were no clearcut symptoms of hyperthyroidism, but the serum iodine concentration was 12.2 micrograms per hundred cubic centimeters. From the history the suspicion is strong that he had true clinical hyperthyroidism with some remission of activity at the time the value for serum iodine was obtained. The number of patients is too small to permit comparison of concentrations of iodine in serum taken in a manic phase with the concentrations of iodine in serum taken in a de-

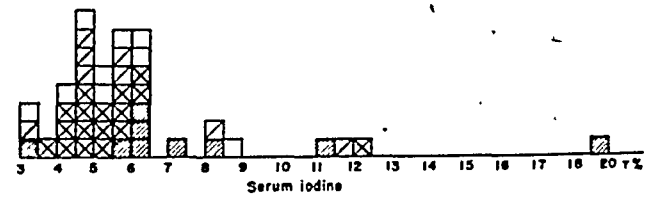



Fig. 1.—Serum iodine concentrations for 26 manic-depressive patients and 17 patients with depression. The barred squares represent values for 9 subjects in the manic phase; the double-hatched squares, values for 17 subjects in the depressed phase of the manic-depressive disturbance; the single-hatched squares, values for 8 subjects with agitated depressions that were not considered manic-depressive disturbances, and the open squares, values for 9 subjects with depressions who did not have a manic-depressive condition.

The 3 patients who had thyroidectomies on our service had initial values for the serum iodine of 11.2, 11.8 and 18.6 micrograms respectively per hundred cubic centimeters.

5. Riggs, D. S., and Man, E. B.: A Permanganate Acid Ashing Micromethod for Iodine Determinations: I. Values in Blood of Normal Subjects, J. Biol. Chem. **134**:193, 1940.

6. Man, E. B.; Smirnow, A. E.; Gildea, E. F., and Peters, J. P.: Serum Iodine Fractions in Hyperthyroidism, J. Clin. Investigation **21**:773, 1942.

7. Man, E. B., and Peters, J. P.: Gravimetric Determination of Serum Cholesterol Adapted to the Man and Gildea Fatty Acid Method with a Note on the Estimation of Lipoid Phosphorus, J. Biol. Chem. **101**:685, 1933. Bogdanovitch, S. B., and Man, E. B.: The Effects of Castration, Theelin, Testosterone and Antuitrin-S on the Lipoids of Blood, Liver and Muscle of Guinea Pigs, Am. J. Physiol. **122**:73, 1938.

pressed phase of a manic-depressive condition. Iodine concentrations for the 17 manic-depressive patients in a depressed phase were not especially

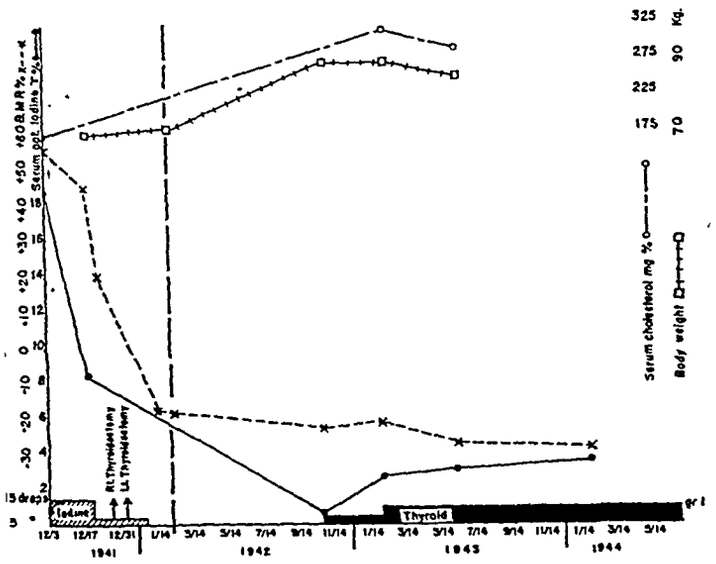



Fig. 2.—Clinical data on patient 1 before and after thyroidectomy.

Before therapy with strong solution of iodine U. S. P., a man aged 36 who had been in a hypomanic state for about two months, had a total serum iodine of 18.6 micrograms per hundred cubic centimeters. His basal metabolic rate could not be definitely established because of his tension, but it was between + 50 and + 60 per cent. His thyroid was enlarged; there was a definite tremor but no exophthalmos. His pulse rate was about 120 per minute. After therapy with strong solution of iodine U. S. P., the precipitable iodine of the serum fell to 8.5 micrograms per hundred cubic centimeters, and his basal metabolic rate, to + 20 per cent. A two stage thyroidectomy was performed. Clinical improvement was pronounced. Tension and anxiety decreased notably. While he was under treatment with the iodine solution, the clinical course, basal metabolic rate and serum iodine levels were typical of hyperthyroidism. Hyperplasia was recognized in the excised gland. There was a decided gain in weight after operation, and eleven months later the basal metabolic rate was —23 per cent. The patient was given 0.5 grain (0.0325 Gm.) of thyroid daily, and after four months this was increased to 1 grain (0.065 Gm.). The patient has continued to take desiccated thyroid and has been able to conduct his business. He has had equivocal symptoms suggestive of mild depression.

low, but, with 2 exceptions, were between 4 and 6.5 micrograms per hundred cubic centimeters.

The values for serum iodine for 3 of the 17 patients of the second group, namely, the depressed patients whose conditions were not diagnosed as manic-depressive, were above the normal range. One of these 3 was the patient who had clinical signs of hyperthyroidism and underwent a thyroidectomy. The serum iodine values for the other 2 patients were between 8 and 9 micrograms per hundred cubic centimeters, a borderline range in which fall a few values for serum iodine of both normal subjects and patients with hyperthyroidism.

In figures 2, 3 and 4 the values for serum iodine and cholesterol, the basal metabolic rates and the body weights of the 3 patients with a clinical diagnosis of hyperthyroidism are shown graphically. The results of administration of strong solution of iodine U.S.P. before operation and of thyroid therapy after operation are also indicated in the figures. The first 2 manic-depressive patients were in a manic phase. After thyroidectomy the man was able to return to his business, and the woman, to her family and housekeeping. The third patient, who was not

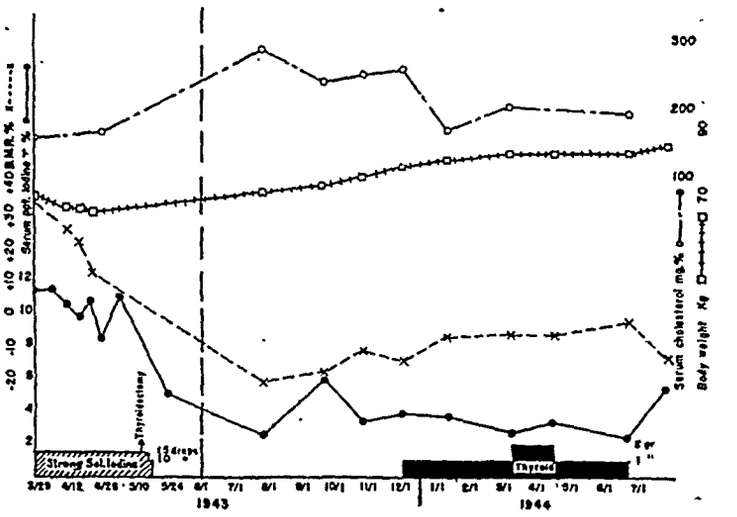



Fig. 3.—Clinical data on patient 2 before and after thyroidectomy.

A woman aged 32 who had shown moderate manic excitement of about three weeks' duration had a basal metabolic rate of + 33 per cent and a precipitable iodine content of the serum of 11.2 micrograms per hundred cubic centimeters. The patient had a diffusely enlarged thyroid, tachycardia, fine tremor, slight lid lag and warm, moist skin. Treatment with strong solution of iodine U. S. P. produced clinical improvement; the basal metabolic rate fell to + 12 per cent, and the precipitable iodine of the serum fell to 8.3 micrograms per hundred cubic centimeters and then rose again to 10.9 micrograms per hundred cubic centimeters. Subtotal thyroidectomy was performed, and examination of the excised gland revealed hyperplasia. After operation her weight increased; the basal metabolic rate fell to —21 per cent, the precipitable iodine of the serum to 2.7 micrograms per hundred cubic centimeters and the serum cholesterol to 295 mg. per hundred cubic centimeters. The patient was given 1 grain of desiccated thyroid, then 2 grains (0.13 Gm.) for a short time and then 1 grain; at present she is not receiving any thyroid. At the time of writing, sixteen months after thyroidectomy, she is able to do her housework and care for her family. She is not manic or overactive. Insufficient time has elapsed to reveal whether thyroid medication should be resumed and continued.

manic-depressive, but had an agitated depression, was less tense and agitated after thyroidectomy, although her depression continued.

COMMENT

The observation that 22 of the 26 manic-depressive patients had serum iodine concentrations within the normal range supports the conclusion that manic and depressive conditions are not usually induced by abnormality in function of the thyroid gland. In fact, all the distinctly abnormal serum iodine concentrations in this series can be explained by the coincidence of a manic-depressive condition and overactivity or underactivity of the thyroid. The average serum iodine concentration for the 17 depressed patients of the manic-depressive group was 5.5 micrograms; that for the 7 patients in a manic phase without hyperthyroidism, 6.1 micrograms, and that for the 16 depressed patients without hyperthyroidism who did not have a manic-depressive disturbance, 5.4 micrograms per hundred cubic centimeters. These averages agree closely with average values for patients without manic or depressive symptoms [2]: The average value for serum iodine for 56 subjects with simple goiter was 6.2 micrograms; for 105 subjects who had no goiter but in whom the possibility of hyperthyroidism was considered, 6.1 micrograms; for 113 patients who did not have myxedema but were suspected of having lowered metabolism, 5.5 micrograms, and for 24 subjects with miscellaneous conditions, 5.3 micrograms per hundred cubic centimeters. For about 29 patients with myxedema the average value for serum iodine before treatment was 1.2 micrograms per hundred cubic centimeters.[3] The average initial serum iodine concentration was 15.2 micrograms per hundred cubic centimeters for 84 patients with hyperthyroidism confirmed at operation.[2] This value of 15.2 micrograms per hundred cubic centimeters is an average one; some of the patients with hyperthyroidism have had initial serum iodine values as low as 9 micrograms per hundred cubic centimeters, while a few patients with mild hyperthyroidism have had serum iodine concentrations between 8 and 9 micrograms per hundred cubic centimeters.

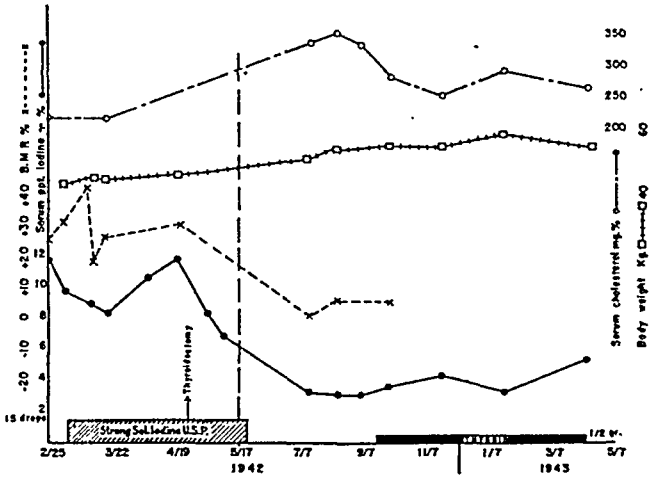



Fig. 4.—Clinical data on patient 3 before and after thyroidectomy.

A woman aged 53 with depression and agitation, which had begun about eighteen months before her admission to the hospital, had a firm nodule in the right lobe of the thyroid. She had a slight tremor but no exophthalmos. She had diabetes, which necessitated her taking about 10 units of regular insulin at the time of admission. The basal metabolic rate was initially only +25 per cent, but about two weeks later, after one week of treatment with a strong solution of iodine U. S. P., it was +42 per cent. The initial level of precipitable iodine in the serum of 11.7 micrograms per hundred cubic centimeters fell to 8.3 micrograms per hundred cubic centimeters after administration of the iodine solution was begun, and then rose again to 11.7 micrograms per hundred cubic centimeters. Thyroidectomy was not performed until seven weeks after treatment with strong solution of iodine U. S. P. was started because the patient's tension and anxiety persisted. The excised gland showed complete involution, with some degenerated adenomatous masses. After operation the anxiety and agitation diminished, but the depression continued. The serum total iodine fell to 3.1 micrograms per hundred cubic centimeters, and the serum cholesterol rose to 354 mg. per hundred cubic centimeters. Administration of ½ grain (0.0325 Gm.) of desiccated thyroid was started and was continued, without relief from the depression. Fifteen months after thyroidectomy the patient was transferred to a sanatorium.

The average serum iodine value of 5.5 micrograms per hundred cubic centimeters for all the depressed patients gives no indication of a relation between hypofunction of the thyroid and a depressive condition. Depressed patients do not present the whole picture of myxedema, which consists of edema, puffy skin, thin coarse hair, hoarse voice, low pulse rate, intolerance to low temperatures and anemia. The assumption that dysfunction of the thyroid is not related causally to the depressive syndrome is supported by the fact that administration of small amounts of desiccated thyroid did not influence the clinical course of patients with depressions. For example, the depression of patient 3, for whom data are presented in figure 4, was not influenced by the administration of desiccated thyroid. A patient with a mild depression, had been given 1½ grains (0.097 Gm.) of thyroid daily for some time. Thyroid therapy was terminated. Six weeks later the depression had not deepened. The values for precipitable iodine in the serum determined when administration of desiccated thyroid was stopped and, again, six weeks later were in the middle of the normal range, and the two values, 6.7 and 6.2 micrograms per hundred cubic centimeters respectively, agreed within the experimental error of the method.

These results seem to show that thyroid overactivity is not instrumental in bringing about a

manic condition. The average serum iodine for 7 manic patients was 6.1 micrograms per hundred cubic centimeters. Two patients with high levels of iodine in the blood had hyperthyroidism, the diagnosis being established by pathologic studies on the glands. The normal values for serum iodine of the manic-depressive patient in a manic phase who did not have hyperthyroidism are in contrast to the findings of Neustadt and Howard.[8] Although 9 patients is a small number on which to base conclusions, it should be emphasized that in a group of 250 to 300 patients determinations of the serum iodine were requested for those persons who were suspected of having abnormal function of the thyroid. The present evidence makes it most probable that the manic state of manic-depressive patients was associated with a high iodine concentration in the serum only in the occasional patients who, in addition, had hyperthyroidism.

A patient may have a manic-depressive disturbance and either hyperthyroidism or hypothyroidism at the same time; yet a manic-depressive disturbance is not necessarily related causally to abnormality in function of the thyroid. In figures 2, 3 and 4 have been presented data on 2 manic-depressive persons and on 1 depressed patient in whom hyperthyroidism and manic or agitated depressive conditions concurred. In all these patients thyroidectomy diminished the overactivity, tension and agitation. It is in the cases of such patients that the danger of not recognizing hyperactivity of the thyroid is paramount.

The incidence in manic and depressive patients of tremor and tachycardia, usually associated with hyperthyroidism; the concurrence of these two syndromes, and the amelioration after thyroidectomy of overactivity, tension and agitation suggest an occasional association of hyperthyroidism and manic-depressive states. Such an association occurs in other conditions; for example, in diabetes and in hyperthyroidism. An association between hyperthyroidism and manic-depressive states has been discussed by Moersch.[9] Their coincidence does not prove thyroid dysfunction to be a causal factor in manic-depressive disturbances. This coincidence is possible, although the function of the thyroid was normal in 22 of 26 manic-depressive patients, as shown by the serum iodine levels. In fact, one might question whether the manic-depressive condition may not play a causal role and induce hyperthyroidism in certain patients. For example, a history of previous episodes of depression in case 2 suggests that the manic-depressive condition was the underlying disturbance in this case. That hyperthyroidism occurred, although hypothyroidism was not observed in the present series of patients, makes one look for the cause of thyroid hyperfunction in these patients. Of course it is true that in any general series of patients studied consecutively, the incidence of hyperthyroidism is greater than the incidence of hypothyroidism. But if hyperthyroidism occurs in patients with manic-depressive disturbances, may not the function of the thyroid have been normal until the manic-depressive cycle interfered with the general physical condition? In our experience it has seemed that the whole biologic system has difficulty in returning to normal function once this manic-depressive cycle has started. If abnormal function of the physiologic system continues, more disorders develop. If the vicious circle can be interrupted before further trouble develops, the patient's return to his normal existence may be hastened.

Whether the manic-depressive state incites overactivity of the thyroid or not, it is important to remember that the two conditions are occasionally present together and are in no sense mutually exclusive. Although certain symptoms of the two disorders resemble each other, the patterns are different. Unless this is remembered, one or the other may be overlooked. The criteria for diagnosis of the two conditions are simply those for the diagnosis of each one separately. However, frequently in the presence of a manic-depressive condition two usual tests for hyperthyroidism are impracticable. The basal metabolic rate and its response to administration of iodine are not reliable. In these patients estimation of the precipitable iodine in the serum before and during administration of iodine has a peculiar value. Determinations of serum iodine would be of similar importance in cases of depression and hypothyroidism, although this combination seems to be a rarer one.

## CONCLUSIONS

Thyroid function was evaluated by measurement of serum iodine concentration in 43 patients with manic or depressive disturbances. Of these, 26 patients had a manic-depressive disturbance and 17 a depressed but not manic-depressive condition.

8. Neustadt, R., and Howard, L. G.: Fluctuation of Blood Iodine in Cyclic Psychoses, Am. J. Psychiat. **99**: 130, 1942.

9. Moersch, F. P.: Psychic Manifestations Associated with Hyperthyroidism, Am. J. Psychiat. **91**:1215, 1935.

A clinical diagnosis of hyperthyroidism was made for 3 of the 43 patients. The values for the serum iodine of 36 of the remaining 40 patients fell within the normal range of 3 to 8 micrograms per hundred cubic centimeters.

Dysfunction of the thyroid cannot be considered as an essential factor in manic-depressive conditions or in manic overactivity or depressed underactivity. There is no way to prove or to disprove that occasionally disturbances of the thyroid may not participate in starting a manic-depressive cycle. In view of the fact that emotions affect the thyroid mechanism, it is conceivable, although the evidence is not yet conclusive, that manic-depressive disturbances may occasionally initiate imbalance of thyroid function.

Prof. John P. Peters and Dr. Alexander W. Winkler, of the Department of Internal Medicine, saw some of these patients in consultation and advised us in this investigation.

Yale University School of Medicine.

# Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

## Physiology and Biochemistry

SALT METABOLISM IN POLIOMYELITIS. JAMES F. RINEHART, J. Nerv. & Ment. Dis. **99**:825 (May) 1944.

Rinehart investigated the possibility that a nonspecific factor lowering the immunity of the host might be responsible for the fact that during an epidemic of poliomyelitis relatively few persons are stricken with the disease. A group of cases of early poliomyelitis were studied with regard to chloride concentration of whole blood and of spinal fluid, packed volume of red blood cells and urinary output of chlorides under controlled intake of sodium chloride. It was found that depletion of chlorides and hemoconcentration were constant. The author believes that these findings represent a preexisting state favoring propagation of the virus and are not simply an effect of the illness. In support of the idea that depletion of salt may predispose to poliomyelitis is the summer incidence of the disease and the fact that often strong, robust children are affected. A history of physical overexertion prior to the onset is frequently present. These factors all lead to salt depletion and dehydration and may predispose to invasion and propagation of the virus of poliomyelitis.

CHODOFF, Langley Field, Va.

IMMEDIATE CIRCULATORY AND RESPIRATORY EFFECTS OF CONVULSIVE SHOCK. LAWRENCE F. WOOLLEY, J. Nerv. & Ment. Dis. **100**:64 (July) 1944.

Woolley reports on a study of the immediate effects on respiration and circulation of metrazol or electrical treatment preceded in each instance by a protective dose of curare. Determinations of the blood pressure and pulse rate were made before treatment, immediately after the injection of curare and every minute thereafter throughout the shock treatment until the values had become stabilized near the patient's norm. Ordinarily there is a considerable elevation in blood pressure and pulse rate prior to the start of the treatment, probably due to anticipatory apprehension. If the curare is not followed by shock, there is a tendency to a gradual fall toward normal over several hours. With deep curarization, there is a period of difficult breathing, and sometimes of stridor, but never respiratory distress or cyanosis. If the metrazol or the electrical current results in a petit mal seizure, a psychic equivalent or an apneic type of reaction, there occurs a fairly pronounced rise in both the blood pressure level and the pulse rate. With a grand mal convulsion, the systolic blood pressure rises during the latent period, reaches a peak during the tonic phase and then rapidly falls toward a normal level. Similar changes occur with the pulse rate. In the period of postseizure excitement there are marked irregularities in pulse rate and blood pressure. The depth of cyanosis occurring during the seizure depends directly on its duration and severity, the amount of mucus in the throat and the intensity of curarization. There is considerable variation in the circulatory and respiratory reactions in different patients and in the same patient during different treatments. It was found that extreme decreases in blood pressure, pulse rate or respiratory rate were promptly overcome by the administration of either epinephrine or neostigmine, thus suggesting that curare plays an important role in these accidents. The author feels that the marked changes in the blood pressure occurring during convulsive therapy may play an important part in bringing about the physical effects which result in postconvulsive confusion and memory defect and which probably contribute to the clinical improvement of the patient.

CHODOFF, Langley Field, Va.

REACTIONS OF MONKEYS OF VARIOUS AGES TO PARTIAL AND COMPLETE DECORTICATION. MARGARET A. KENNARD, J. Neuropath. & Exper. Neurol. **3**:289 (July) 1944.

Kennard reports her observations on the reactions of monkeys following the removal of extensive portions of the cortex. Twenty-five Macaca mulatta monkeys were used, of which 18 were infants of dated birth in the first few months of life and 7 were either immature or adult animals. Only 4 of these animals were totally decorticated; but 12 of the remaining 21 were deprived, by cortical operation, of all "voluntary" motor power. The remaining 9 monkeys served as controls.

Kennard reports that the decorticate adult Macaca has a motor performance limited to the simpler righting reflexes which alter the posture of its extremities as its position in space is changed. It is moderately spastic and relatively less motile than the decorticate infant. The latter is able to right itself, to maintain a standing posture and to walk spontaneously. Activities such as sucking, swallowing, vocalizing or clinging are more complex and less stereotyped than those of the adult. Spasticity is absent, and the posture at rest is one of exaggerated flexion.

It is clear that removal of the frontal association areas, areas 8, 6 and 4, the parietal areas and the basal ganglia from infant monkeys has some effect on reactions in infancy. The observations indicate the presence of some cortical function at an early age. The infant cortex has a greater capacity for reintegration of motor activity than has the cortex of the adult Macaca. Also, reorganization of the cortex injured in infancy follows a pattern which is fixed both by the age of the animal and by the size and site of the lesion.

GUTTMAN, Philadelphia.

THE MECHANICS OF TRAUMA WITH SPECIAL REFERENCE TO HERNIATION OF CEREBRAL TISSUE. A. H. S. HOLBOURN, J. Neurosurg. **1**:190 (May) 1944.

On the assumption that the brain behaves like an elastic body, Holbourn attempts to establish a theory for the pathogenesis of traumatic cerebral cysts. He introduces his thesis by establishing the basic concepts of the theory of elasticity: 1. Stress means force per unit area. 2. Strain is the displacement of a body as a consequence of stress. 3. Hydrostatic pressure (e. g., intraventricular cerebrospinal fluid pressure) is a simple type of stress. 4. A force acting tangential to a surface is a shearing stress, and its resultant strain is a distortion of the object to which the stress is applied (unlike hydrostatic pressure).

The foregoing theory may be applied to inanimate matter: If enough stress is applied to a substance, that substance will not recover its original shape from the resultant distortion strain; i. e., elastic resilience fails when the shearing stress exceeds a certain critical value. By a priori reasoning, the author applies the theory of elasticity to the brain, which he regards as similar to inanimate matter. If the stress only slightly exceeds the critical value, a cerebral "crack" occurs, with repair by glial scarring. If the stress is high, there is a greater liability for the increased distortion to produce a cerebral cyst; i. e., the cerebral tissues are torn apart.

Lastly, the author applies the theory of elasticity to herniation of the brain through an opening in the skull due to intraventricular pressure. He demonstrates the appropriateness of the application by using a photoelastic gelatin model. He was able to predict the positions and shapes of the injured regions of the brain, and his predictions were found to coincide with the actual pathologic changes observed by other investigators.

WHITELEY, Philadelphia.

## Diseases of the Brain

TRAUMATIC PNEUMOCEPHALUS WITH SPONTANEOUS VENTRICULOGRAMS. ABRAHAM KAPLAN, J. Neurosurg. **1**:166 (May) 1944.

Cerebrospinal rhinorrhea with pneumocephalus may have various causes but usually is secondary to fracture of the posterior wall of the frontal sinus or the cribriform plate of the ethmoid bone. Through a tear in the adjacent meninges air enters the subarachnoid space; it may become trapped in the subdural, subarachnoid or ventricular spaces, or even in the brain substance. Meningitis is the most serious complication. Treatment consists of rest, dependent posture, decrease in intracranial pressure, administration of sulfonamide compounds and surgical repair when needed.

The author reports a case in which rhinorrhea appeared after twenty-nine days and spontaneous pneumoventriculograms were obtained.

WHITELEY, Philadelphia.

EXPERIMENTAL TRAUMATIC CEREBRAL CYSTS IN THE RABBIT. MURRAY A. FALCONER and DOROTHY S. RUSSELL, J. Neurosurg. **1**:182 (May) 1944.

Beneath the center of experimental decompression areas in rabbit skulls, 50 per cent of the brains showed pathologic changes in the subcortical white matter, and 30 per cent, cyst formation. Edema, hemorrhages, softening and cavitation all usually appeared within one week after operation. At the end of two to seven weeks the walls of the cysts had become lined with glia. At the medial lip of the artificially produced herniation of the brain, a scar usually extended from the wall of the cyst to the surface of the brain.

The authors conclude that all these changes have a structural basis, since they always occured at or just beneath the junction of the cortex and the white matter; that is, lines of cleavage during physical strains result at the sites of transition in tissue consistencies. But splitting of tissues must always be preceded by certain pathologic changes, with resultant softening of the brain.

The authors believe these studies may have some bearing on the pathogenesis of traumatic cerebral cysts in man.

WHITELEY, Philadelphia.

RUPTURE OF A LEFT TEMPOROSPHENOIDAL BRAIN ABSCESS INTO THE VENTRICLE. LOUIS E. WOLFSON, New England J. Med. **230**:170 (Feb. 10) 1944.

Wolfson reports the case of a 56 year old man who had chronic infection of the left mastoid for fifty-one years. After an acute infection of the upper respiratory tract, an exacerbation of the mastoiditis developed, and a radical mastoidectomy was performed on that side. Sulfadiazine therapy was given. Cultures of pus from the mastoid area revealed Staphylococcus albus and a nonhemolytic streptococcus.

Five days after operation right hemiparesis and stupor developed. The mastoidectomy wound was reexplored, and the underlying dura was found to be tense. The dura was incised, as was the brain, and a cannula was inserted for a distance of 3 cm., when pus was obtained (Staph. aureus, diphtheroids and a nonhemolytic streptococcus). Clinical recovery was prompt, and the level of sulfadiazine in the blood was maintained at about 10 mg. per hundred cubic centimeters.

Subsequently, iodized poppyseed oil was injected into the cavity of the abscess, and roentgenograms indicated that it communicated with the left lateral ventricle.

Wolfson states that the use of a high concentration of sulfadiazine probably checked further spread of the infection. Rupture of such an abscess is extremely rare and is generally seen only at autopsy. Roentgenograms showing such an event during life have not heretofore been reported on.

GUTTMAN, Philadelphia.

APPERCEPTIVE BLINDNESS IN LISSAUER'S DEMENTIA PARALYTICA. MARY T. PATTERSON and E. STENGEL, J. Neurol. & Psychiat. **6**:83 (July-Oct.) 1943.

Patterson and Stengel report a case of Lissauer's dementia paralytica in which apperceptive blindness was a prominent feature and was correlated anatomically with accentuation of the paretic changes in the parastriatal areas of the occipital cortex. The authors interpret the apperceptive blindness as a reaction of denial of chaotic visual impressions of the outer world, resulting from interaction of a severe thought disorder, lack of attention, inability to focus and visual agnosia. The psychologic mechanisms underlying apperceptive blindness are similar to those of Anton's symptom of unawareness of cortical blindness, and both have much in common with psychoneurotic symptoms.

MALAMUD, Ann Arbor, Mich.

TRAUMATIC DILATATION OF THE CEREBRAL VENTRICLES. D. W. C. NORTHFIELD, J. Neurol. & Psychiat. **7**:1 (Jan.-April) 1944.

Traumatic dilatation of the ventricles may be divided into three types: (1) local bulging, resulting from focal contusion of the brain; (2) enlargement of the whole of one lateral ventricle, either ipsilateral or contralateral to the site of injury, and (3) general symmetric enlargement of both lateral ventricles. Northfield discusses the possible mechanisms involved in the last two forms. These types of ventricular dilatation may result either from disturbances in the cerebrospinal fluid system or from atrophy of the brain tissue. The former may arise from excessive production, delayed circulation or impaired absorption of the cerebrospinal fluid. While excessive production due to injury is improbable, there are clinical and histologic evidences that blood in the cerebrospinal fluid system leads to occlusion of

the leptomeningeal spaces, scarring of the cortex and resulting dilatation of the ventricles. The weight of evidence, however, indicates some change occurring primarily in the brain tissue which leads to atrophy and in this way to hydrocephalus ex vacuo. Generalized cerebral edema has not yet been proved to be a cause of such atrophy. A number of observations suggest that in cases of severe trauma a temporary excessive outpouring of fluid from the choroid plexus takes place. Through transient delay of circulation and absorption, due to the presence of blood and a traumatized ependyma, this fluid penetrates the wall of the ventricle and passes into the brain tissue; there, by impairing its nutrition, it leads to edema and ultimately to gliosis and atrophy.

N. MALAMUD, Ann Arbor, Mich.

CONGENITAL CYST IN THE LEFT TEMPORAL LOBE. S. OBRADOR, F. PASCUAL DEL RONCAL and M. FALCÓN G., Arch. de neurol. y psiquiat. de Mexico **6**:385 (Sept.-Oct.) 1943.

A 27 year old woman complained of persistent frontal and occipital headache and recurrent attacks of vertigo, of five months' duration. There were a few attacks of transitory blurring of vision. A lumbar puncture made soon after the onset relieved her symptoms for one month. Occasionally she felt as though her limbs did not exist. Loss of consciousness, without convulsive movements, occurred once.

Examination showed bilateral papilledema, right homonymous hemianopsia, weakness of the lower right side of the face, a tendency to veer to the left in the Romberg position and some inward drift of the outstretched right upper limb. The patient showed mild euphoria, some intellectual enfeeblement and amnestic aphasia. There were abnormally slow waves (4 to 5 per second) of low voltage in the left temporo-occipital region and a few delta waves in the right frontal area. Pneumoencephalographic examination showed that the right ventricle was enlarged and displaced to the right and that a small amount of air was present in the posterior portion of the left ventricle, which seemed to be pushed upward and backward.

Operation showed a voluminous cyst with white, smooth walls and poor vascularization, in the subcortex of the left temporal lobe. The cyst was more than 6 cm. in diameter and was filled with cerebrospinal fluid. No tumor nodules were found. Biopsy of a small piece revealed the wall of a cystic cavity lined with ependyma; there were a few amyloid bodies and mild neuroglial proliferation in the wall. The authors consider that this cyst was congenital and that at one time it was connected with the wall of the lateral ventricle.

SAVITSKY, New York.

## Diseases of the Spinal Cord

CHORDOMATA: A REVIEW OF THE LITERATURE, WITH REPORT OF A SACROCOCCYGEAL CASE. DANIEL B. FAUST, HUGH R. GILMORE JR. and CHARLES S. MUDGETT, Ann. Int. Med. **21**:678 (Oct.) 1944.

Faust, Gilmore and Mudgett review the literature of chordomas and report an additional case. The survey indicates the following distribution of recorded lesions: cranial, including spheno-occipital and nasopharyngeal, 92; vertebral, 34; caudal or sacrococcygeal, 122, and others, 4. Thus, 48.4 per cent of the reported lesions were in the sacrococcygeal region and 36.5 per cent in the cranial region. With few exceptions, most of the remaining 15.1 per cent of the lesions were located along the vertebral column.

The signs and symptoms of cranial chordoma are those of any intracranial neoplasm or of a tumor of the nasopharyngeal cavity. Chordomas involving the vertebral or the sacrococcygeal region do not produce symptoms or signs which differ from those of any other neoplasm. The lesions may be relatively benign but are more frequently malignant, with or without metastases. Successful surgical removal depends on the location and the size of the lesion. Both roentgen and radium therapy are of questionable value. A fatal termination in the course of one to six years is the rule, but cures following surgical intervention have been reported.

Faust, Gilmore and Mudgett report the case of a 23 year old Negro who had a large sacrococcygeal chordoma, extending into the right lower quadrant of the abdomen, with extensive pulmonary and adrenal metastases.

GUTTMAN, Philadlephia.

PATHOLOGY, CLINICAL MANIFESTATIONS AND TREATMENT OF LESIONS OF THE INTERVERTEBRAL DISKS. ALBERT OPPENHEIMER, New England J. Med. **230**: 95 (Jan. 27) 1944.

Oppenheimer reports on the pathologic process, clinical manifestations and treatment of lesions of the intervertebral disks. He observed 826 patients with lesions of disks, a control series of 200 persons without symptoms and another control series of 100 patients with complaints suggestive of such lesions. An attempt was made to correlate the clinical and anatomic findings and to evaluate various methods of management and treatment of these lesions.

The author concludes that the high incidence of lesions of the disks may be explained by the evolutionary development of the human spine. The system of bones and joints, originally adapted to bear almost no vertical stress, sustains in man the whole impact of the upright posture and locomotion. Regardless of the cause of flattening of the intervertebral disk, narrowing of the corresponding intervertebral spaces results, associated with displacement of articular processes, narrowing of the neural foramen and abnormal contact between vertebral bodies.

The clinical manifestations depend on the anatomic changes described rather than on the degree of thinning of the disk. Narrowing of the neural foramen may induce radicular pain, but compression of the nerve roots does not always occur, owing to the variable relationship between the caliber of the nerve and the degree of impingement. Pain in the back and limitation of vertebral movements are less frequent (about 20 per cent) and seem to be caused predominantly by involvement of the apophysial joints as a result of a lesion of an intervertebral disk. In most cases lesions of disks produce symptoms felt in the limbs, and not in the back or neck.

The signs and symptoms of radicular neuralgia and neuropathy are often indistinguishable from those of myalgia, arthritis, bursitis and referred visceral pain. The differential diagnosis can be made only after exhaustive clinical survey.

Oppenheim states that surgical removal of a ruptured disk followed by spinal fusion did not always prevent the development after several years of symptoms caused by subsequent thinning of the disk. Conservative treatment yielded satisfactory results in about 75 per cent of cases.

GUTTMAN, Philadelphia.

MYELITIS DUE TO VACCINATION. G. J. DIXON, J. Neurol. & Psychiat. **7**:18 (Jan.-April) 1944.

Dixon reports the case of a man aged 27 who had fever, muscular pain and unsteadiness of gait nine days after primary vaccination. After a temporary remission, there was sudden onset of paraplegia on the twenty-third day after vaccination. There was gradual and almost complete recovery in six months. The case differs from cases of classic postvaccinal encephalitis in that the symptoms were spinal rather than cerebral.

N. MALAMUD, Ann Arbor, Mich.

BRACHIAL PAIN FROM HERNIATION OF CERVICAL INTERVERTEBRAL DISC. F. A. ELLIOTT and MICHAEL KREMER, Lancet **1**:4 (Jan. 6) 1945.

Elliott and Kremer report 8 cases of brachial pain caused by herniation of the sixth cervical intervertebral disk. The pain was in the back of the shoulder, down the back of the arm and along the radial border of the forearm and sometimes in the upper pectoral region. There were paresthesias in the thumb and the index and middle fingers. In some cases there was a history of acute stiff neck. The signs include limitation of movement of the neck; pain produced in the arm by movements of the neck and by downward pressure on the head, and tenderness, weakness and wasting of the pectoralis major, triceps and extensor muscles of the wrist and fingers. The triceps jerk was reduced or absent, and there was usually hypalgesia over the thumb and the index finger.

The clinical picture was that of a lesion of the seventh cervical root. Trauma was not an essential precursor of the syndrome, and even when present it was often of minor degree. Myelographic examination with a contrast medium in 3 cases showed a filling defect opposite the sixth intervertebral disk, involving the seventh cervical root on the affected side. Treatment was conservative. However, the authors conclude that if conservative measures of fixation and traction of the head do not succeed in eliminating the pain surgical intervention is indicated.

YASKIN, Camden, N. J.

## Peripheral and Cranial Nerves

MULTIPLE PERIPHERAL NEURITIS OCCURRING WITH SULFONAMIDE THERAPY. M. A. BLANKENHORN, Ann. Int. Med. **20**:423 (March) 1944.

Blankenhorn found multiple peripheral neuritis in 6 of a total of 600 patients who were given sulfonamide therapy. Three of the patients had chronic alcoholism, and a fourth was thought to have the condition. Three patients gave a history of a poor diet and showed evidence of hypovitaminosis.

Blankenhorn also reported on 8 patients who presented evidence of neuritis before a sulfonamide drug was administered. In this group, only 1 patient's symptoms became more pronounced after the sulfonamide therapy. The author concludes that the administration of vitamins may have prevented the neuritis from becoming aggravated.

GUTTMAN, Philadelphia.

TONSILLECTOMY AND POLIOMYELITIS: ONE CASE OF POLIOMYELITIS FOLLOWING 8,915 TONSILLECTOMIES. JOHN RANDOLPH PAGE, Arch. Otolaryng. **39**:323 (April) 1944.

Page obtained data from the department of health of the city of New York showing the number of cases of poliomyelitis that occurred in the five years from 1937 to 1941 inclusive. The disease was most prevalent in 1937, 1939 and 1941, the number of cases during those years being 243, 184 and 404, respectively. All patients who had undergone tonsillectomy in the Manhattan Eye, Ear, Nose and Throat Hospital during these three years were communicated with by mail. A total of 27,849 postal cards were sent out, with a return card attached. Two questions were asked: 1. Have you had any illness since the tonsillectomy? 2. What were the nature and date of illnesses, if any?

A total of 8,915 replies were obtained, and among them 1 case of poliomyelitis was reported. The case occurred in a 7 year old boy about one month after his tonsils and adenoids had been removed.

RYAN, M.C., A.U.S.

SUTURELESS REUNION OF SEVERED NERVES WITH ELASTIC CUFFS OF TANTALUM. PAUL WEISS, J. Neurosurg. **1**:219 (May) 1944.

The following advantages in linking severed nerve stumps with closely fitting sleeves appear to be attained. 1. Absence of sutures permits nerve fibers to regenerate in a strictly longitudinal direction and avoids the formation of adhesions due to tissue reaction. 2. Dissipation of fluid necessary for nerve regeneration is prevented. 3. Adhesions between the nerve junction and the surrounding tissues are prevented.

Weiss has devised a method whereby normally unelastic tantalum foil can be annealed to the elasticity and resilience necessary to form it into tight, permanent wound sleeves. These sleeves are closely fitted around the approximated nerve ends, and the aforementioned advantages are attained.

Eleven experimental animal unions were assayed, with 9 good results from an anatomic viewpoint. The functional results will be reported later.

WHITELEY, Philadelphia.

ELECTROMYOGRAPHIC STUDIES OF MUSCLE DYSFUNCTION IN INFECTIOUS POLYNEURITIS AND POLIOMYELITIS. MARY A. B. BRAZIER, ARTHUR L. WATKINS and ROBERT S. SCHWAB, New England J. Med. **230**:185 (Feb. 17) 1944.

Brazier, Watkins and Schwab studied 10 cases of infectious polyneuritis (so-called Guillain-Barré-Strohl syndrome) and compared the findings with those in a similar number of cases of poliomyelitis and of traumatic nerve lesions. The authors conclude that their studies revealed the following similarities of muscle dysfunction in infectious polyneuritis and poliomyelitis: Muscular tenderness and paresis were characteristic of both diseases, and the electrical abnormalities in both conditions were correlated with weakness rather than with "sensitivity." Partially paralyzed muscles showed hyperirritability when stretched; this was relieved by hot fomentations. The authors conclude that paretic muscles are hyperirritable even when at rest, with discharging electrical potentials characteristic of regenerating motor units. Reciprocal innervation was frequently disrupted in cases of polyneuritis and poliomyelitis, with consequent simultaneous activation of opposing muscles. This phenomenon was attributed to pain, associated with activity or motion.

The disorganization of reciprocal innervation was not so marked in the cases of polyneuritis because the

simultaneous activation of opposing muscles in this disease was not characterized by synchrony of component discharge.

GUTTMAN, Philadelphia.

POST-TRAUMATIC PAIN AND THE CAUSALGIC SYNDROME. J. DOUPE, C. H. CULLEN and G. Q. CHANCE, J. Neurol. & Psychiat. **7**:33 (Jan.-April) 1944.

The causalgic syndrome is characterized by persistent severe pain in the hand or foot following an injury to a limb despite the absence of apparent cause. Pain is the central feature of the syndrome, while nutritional disturbances in the form of changes in the skin or osteoporosis of the bones may or may not be associated. The authors are of the opinion that causalgic pain is due to the activation of sensory fibers by efferent impulses in the sympathetic fibers. This view is based on the following facts: 1. The pain is spontaneous, the result of alternating activities of sudomotor and vasoconstrictor fibers; it is thus related to the needs of thermoregulation rather than to any external or local influence. 2. The pain is diffuse and is described as hot and burning because the small fibers for pain and temperature sensation are sensitive to the action currents of the sympathetic fibers. 3. Emotional excitement or stimulation aggravates the pain because of the associated discharge in sympathetic fibers. 4. A tendency to profound mental changes exists. 5. The causalgic pain is relieved by sympathetic block. This theory also serves to explain the increased blood flow in the painful limb, since stimulation of afferent fibers causes antidromic vasodilatation, while the changes in the skin are caused by vasodilatation and disuse.

On the basis of these principles, the authors report a series of cases illustrating three types of post-traumatic pain: (1) psychogenic, (2) causalgic and (3) dystrophic. The results of therapeutic test, together with other neurotic features, serve to distinguish the psychogenic from the other types. The causalgic type may be further classified as proximal or distal, depending on whether the pain originates at the site of the nerve lesion or near the termination of the fibers, the distal form being due to edema or ischemia. Dystrophic pain is secondary to disturbances of nutrition resulting from such factors as disuse, defective arterial supply and defective venous or lymphatic drainage.

MALAMUD, Ann Arbor, Mich.

## Treatment, Neurosurgery

REHABILITATION OF THE NERVOUS SYSTEM IN WAR TRAUMA. A. R. LURIA, Am. Rev. Soviet Med. **2**:44 (Oct.) 1944.

Luria bases his observations on the work at the neurosurgical rehabilitation clinic of the All-Union Institute of Experimental Medicine and the Convalescent Hospital. The problem of rehabilitation is to direct and organize functional recovery. Rehabilitation becomes an independent branch of medicine, having its own rationale and requiring its own methods.

Of all war casualties, 8 per cent involve nerve injuries. Their importance lies in the severity and extent of functional damage. Luria stresses the fact that functional recovery is not always hopeless, and study reveals that specific treatment may help the patient regain impaired function, even partially, without waiting for nerve regeneration to be completed. Functional disturbance after nerve injury is produced by at least two components: (1) local nerve palsy and (2) associated inhibition of a functional nerve aggregate. Surgical intervention is the first step in rehabilitation.

Luria states that the training of isolated muscle groups through various mechanotherapeutic measures, gymnastics and motor stimulation by galvanotherapy are insufficient for rehabilitation. Experience at the Convalescent Hospital shows that directed objective movements, and not isolated mechanical ones, possess the necessary organizing function. The leading place in a system of rehabilitation therapy for peripheral nerve palsy must be occupied by planned work or by occupational therapy. The planned movements depend little on specific muscles and can be executed by various combinations of other muscle groups. Instruments especially adapted to injured hands were made in the recovery clinic. The most successful results were obtained when the tool was modified to accommodate improvements and to stimulate further activity on the part of the injured extremity.

Rehabilitation following injuries to the brain is based on the "transference of function" to another system, e. g., the substitution of touch for sight or the use of the good hand for that of the paralyzed one. "This 'substitutive' compensation requires directed and prolonged exercises, to train new nerve centers for precise work." However, this shift is not the only therapeutic measure for the treatment of cerebral injuries. The complex function of the brain is to some extent as independent of separate fixed cerebral areas as is planned movement of any single muscle. By location of an impaired functional link and by substitution of a new one, recovery is instituted.

Luria concludes that damage to the brain does not necessarily lead to a hopeless functional defect. Every act follows a certain pattern, and the functional system is remarkable for its considerable plasticity. This is the basis for reconstruction therapy. In many instances, defects arising from war trauma are overcome, and the patient regains, to some degree, his lost working capacity.

GUTTMAN, Philadelphia.

MIGRAINE HEADACHES RELIEVED BY HYPOGLYCEMIC REACTION. SIDNEY J. TILLIM, Ann. Int. Med. **20**:597 (April) 1944.

Tillim reports 2 cases in which the patients were treated for migraine with injections of ergotamine tartrate, inhalations of pure oxygen or oxygen and 7 per cent carbon dioxide, intravenous injections of thiamine hydrochloride, histamine desensitization and administration of various glandular preparations, with little or no success. Both the patients became addicted to opiates. The author observed that intravenous injections of insulin promptly and fully aborted the migraine attacks which occurred during hospitalization. He states that induced hypoglycemia is antispasmodic and antagonistic to sympathetic activity and concludes that this action relieved the headaches.

GUTTMAN, Philadelphia.

A PRELIMINARY REPORT ON A METHOD FOR LENGTHENING THE EFFECT OF A SYMPATHETIC NERVE BLOCK. FERDINAND C. LEE, DAVID I. MACHT and ROSS Z. PIERPONT, Bull. Johns Hopkins Hosp. **74**:119 (Feb.) 1944.

Lee, Macht and Pierpont report on a method for prolonging the effect of a sympathetic nerve block. Paravertebral injections of 10 cc. of peanut oil containing 4 per cent monobromohydroxybenzyl alcohol were given 26 elderly patients with arteriosclerosis. In 24 patients

the temperature of the foot did not increase until three hours after the injection, and then the limb remained warm for about five days. At the end of eight days the beneficial effect disappeared. In 1 patient the total effect persisted about four days, while in the remaining patient no response was noted.

The method was developed primarily to avoid the almost daily injections for the treatment of thrombophlebitis, but the authors believe that it may prove helpful in any case in which improved circulation in the extremities is required. GUTTMAN, Philadelphia.

THE EXCRETION OF PENICILLIN IN THE SPINAL FLUID IN MENINGITIS. DAVID H. ROSENBERG and J. C. SYLVESTER, Science **100**:132 (Aug. 11) 1944.

Rosenberg and Sylvester administered penicillin in doses of 20,000 to 40,000 Oxford units intravenously and intramuscularly to 8 patients with meningitis. For 6 of these patients the condition had been proved to be meningococcic meningitis. Sixty to one hundred and forty minutes after administration penicillin was recovered from the cerebrospinal fluid, following lumbar puncture, in concentrations of 0.03 to 0.35 unit per cubic centimeter.

These data suggest that penicillin administered intravenously or intramuscularly in adequate doses may be effective in the treatment of meningitis without supplementary intrathecal therapy.

GUTTMAN, Philadelphia.

PROSTIGMINE AND EPHEDRINE IN MYASTHENIA GRAVIS. A. WILSON and H. B. STONER, Lancet **1**:429 (April 1) 1944.

Wilson and Stoner treated a series of 10 patients with parenteral injections of neostigmine methylsulfate and oral administration of neostigmine bromide, given alone or with ephedrine. Ephedrine given alone, either orally or subcutaneously, was also tried. Their results supported the observations in previous work in demonstrating that patients treated with the two drugs together gave more prolonged clinical responses than patients treated with neostigmine alone. "In all cases combined parenteral administration increased the degree and duration of relief from symptoms." The addition of ephedrine was particularly effective in alleviating diplopia and asthenia; in some cases ergographic records confirmed the latter effect, and often the patients themselves volunteered the information that they felt an increase in general muscular strength. Ephedrine given alone helped only 1 patient to any degree.

The cholinesterase activity of the serum was studied, and its inhibition during treatment was found to parallel, but not necessarily to equal in degree, the clinical change. The authors felt that the extra benefit derived from taking ephedrine could not be attributed to a change in cholinesterase activity alone.

The clinical effects of neostigmine were attributed both to the neutralization of a substance circulating in the blood which produces a partial block in neuromuscular transmission and to the inhibition of cholinesterase activity. The extra benefit derived from ephedrine when given with neostigmine was thought to be gained through prolongation of an epinephrine effect. Whether that effect takes place by augmenting "the action of acetylcholine protected by prostigmine, or whether adrenaline potentiates the anti-curare action of prostigmine is a question which can be settled only by further investigation." McCARTER, Philadelphia.

## Encephalography, Ventriculography, Roentgenography

NORMAL AIR ENCEPHALOGRAMS IN PATIENTS WITH CONVULSIVE SEIZURES AND TUMOR OF THE BRAIN. H. HOUSTON MERRITT and CHARLES BRENNER, New England J. Med. **230**:224 (Feb. 24) 1944.

Merritt and Brenner report the histories of 3 patients (38, 27 and 19 years old) who suffered from convulsive seizures and had normal pneumoencephalograms seven, twenty and thirty months, respectively, after their first convulsion. A cerebral tumor was subsequently found in each case. All the tumors were astrocytomas—1 in the left temporal lobe, 1 in the right motor area and 1 in the right frontal lobe.

The authors conclude that although cerebral tumor is among the rarer causes of convulsive seizures, such a tumor may cause convulsive seizures without producing any demonstrable distortion of the ventricular system. A cerebral tumor is not likely to produce any change in the ventricular system unless it is large enough to produce focal neurologic signs or signs of increased intracranial pressure. If, in the absence of these signs, it is decided that an air study is advisable, a negative report should not be accepted as conclusive proof that no tumor is present. GUTTMAN, Philadelphia.

SOME CONSIDERATIONS CONCERNING THE ROENTGEN DIAGNOSIS OF SKULL FRACTURES. J. C. KENNING and IVOR D. HARRIS, Radiology **41**:532 (Dec.) 1943.

Kenning and Harris review 9,000 roentgenograms revealing fracture of the skull. Four routine exposures were made: two lateral views and a frontal and an occipital view. Additional exposures were made in questionable cases.

The fractures were divided into three groups: (1) those in the anterior third of the skull, involving the frontal area; (2) those in the middle third, involving the parietal, sphenoid, temporal and mastoid area, and (3) those in the posterior third, involving the occipital bone. Of the fractures, 26.8 per cent were in the anterior third, 45.3 per cent were in the middle third and 27.9 per cent were in the posterior third.

Roentgenographic differentiation of linear fractures from suture lines, diploic markings, vascular grooves and artefacts is often difficult. Sometimes only by careful study is the differentiation made. Fractures of the middle third are the most easily missed.

Complicating fractures of the anterior third include involvement of the cribriform plate of the frontal sinus, with an occasional aerocele, and involvement of the optic foramen. In the middle third, one may see involvement of the sphenoid sinus and the mastoid. Bony nonunion of fractures of the mastoid may persist indefinitely. Involvement of the foramen magnum may be seen with fractures of the posterior third.

TEPLICK, Philadelphia.

TABETIC ARTHROPATHY OF THE HIP. IRVING WALIN, Radiology **42**:79 (Jan.) 1944.

Walin reports a case in which neurogenic arthropathy (Charcot joint) was followed from its incipiency.

A white woman aged 57 had the original roentgenograms made because of dislocation of the left hip. Postreduction roentgenograms revealed that the hip joint was normal. Seven weeks after reduction the

hip again became dislocated, without trauma. A brace was applied. Roentgenograms made seven months after the original dislocation revealed extensive ossification of the joint capsule. Five months later another spontaneous "slipping" occurred. Roentgenograms at this time revealed typical neurogenic arthropathy with disruption of the head and fragmentation. The proximal head of the femur was dislocated superiorly.

TEPLICK, Philadelphia.

KLIPPEL-FEIL MALFORMATION. WILLIAM E. ALLEN JR., Radiology **44**:79 (Jan.) 1945.

The Klippel-Feil anomaly is characterized by absence or shortening of the neck, lowering of the hair line and limitation of motion of the neck, especially lateral bending. All or most of the cervical vertebrae may be fused. A large number of associated anomalies and deformities of the cervical vertebrae are commonly seen.

The author reports a case of this anomaly in a 24 year old soldier, whose sole complaint was a small tumor on the right shoulder which caused him some difficulty in carrying a pack. The following fifteen deformities and anomalies were seen in the roentgenograms: (1) elevation of the right scapula; (2) fusion of the first cervical vertebra and the occiput; (3) fusion of the bodies of the second and third cervical vertebrae; (4) fusion of the spinous processes of the second and third cervical vertebrae; (5) narrowing of the body of the fourth cervical vertebra; (6) spina bifida occulta of the bodies of the fourth and seventh cervical vertebrae; (7) bifid spinous process of the fifth cervical vertebra; (8) partial fusion of the bodies of the seventh cervical and first dorsal vertebrae; (9) dorsal hemivertebra; (10) deformed bodies of the upper dorsal vertebrae; (11) kyphosis and scoliosis of the dorsal portion of the spine to the right; (12) right cervical rib; (13) fusion of the first and the second rib on the right; (14) rudimentary right twelfth rib, and (15) thinning of the left fifth rib posteriorly.

TEPLICK, Washington, D. C.

# Society Transactions

## ILLINOIS PSYCHIATRIC SOCIETY

DAVID SLIGHT, M.D., *President*

*Regular Meeting, May 6, 1944*

**Group Psychotherapy in Mental Institutions.** DR. J. W. KLAPMAN, Chicago.

An important instrument of treatment fast emerging into general use wherever large number of patients are being cared for is the practice of group psychotherapy.

Its therapeutic effects are mediated largely through the influence of group emotion and group formation, and one of the first clear expositions of this group emotion was given by Freud, in his "Mass Psychology and the Analysis of the Ego." Freud confined himself to one type of group formation—that in relation to a leader. Redl amplified the subject and showed that group emotion may crystallize about a person who could in no sense be regarded as the leader; it may even crystallize about a person outside the group. Redl called such a person—the focus of group emotion—"the central person," but not necessarily its leader. In this there is no fundamental conflict between Freud and Redl, but the latter has expanded and amplified the range of group emotional factors.

In group psychotherapy the author finds predominantly active as group emotional formation a combination in various degrees of three types of Redl's group formations: (1) the patriarchal sovereign type, (2) the leader type, the group formation corresponding most closely to Freud's conception, and (3) the tyrant type.

The types described by Redl do not represent the whole possible range of group formations but are a few samples. As samples, they are described in more or less "pure culture." In the actual practice of group therapy one finds elements of these formations occurring in various combinations, depending on the personality of the therapeutist, the character of the group and any special circumstances surrounding the therapy. If the therapeutist becomes too stringent in his supervision, there is a melting away of spontaneity. If he is too permissive and narcissistic, drives become overtly manifest, interest will lag and group formation of utilizable transferences will be sensibly impaired. But under favorable conditions there is a perceptible transference to the therapeutist and from patient to patient because there is emotional acceptance, more or less, of interpretations which one could hardly conceive of on the basis of the transitory individual relationships as they occur in the usual ward practices of a large institution for mental diseases. Moreover, the patient to patient relationship carries over even into the post-hospitalization existence, as witness the tendency to form ex-patient societies and associations.

In group therapy patients' problems are subjected to a process of intellectualization or objectification. Consciousness and intellect, being a great relaying center between the external world and the more organically associated drives, has an important function in personality homeostasis. Thus, insights acquired in class exert a soft, but steady, pressure.

Usually group psychotherapy is administered by a series of lectures. Believing that in a large mental institution it is necessary to have ready access to a body of information designed to further reeducation and education, even in the academic sense, and recognizing, furthermore, that it may become necessary to change therapeutists on short notice, the author has devised a mimeographed textbook to be used in class. Patients read passages aloud in class and then summarize and comment on what they have read. The therapeutist amplifies and interprets. This frequently leads to interesting digressions, which, in turn, may be the start of symposiums, such as one recently held by a number of patients on the question, "What Is an Open Mind?" Other assignments and book reports are part of the class work. Demonstrations of subject matter are made wherever possible. For example, when the group is studying the chapter on biology, it is taken for a tour of the clinical laboratory and shown slides of tissue cells and germs under the microscope.

The results of group psychotherapy, easily appreciated, are difficult to evaluate objectively in terms of statistics. One reason is that one must abstract qualitatively and quantitatively the spontaneous recoveries and improvements. Second, when, as at the present time, most patients who show any reasonable hope of a favorable outcome are treated with shock therapies, the effects of such treatment must be abstracted from the possible results of group psychotherapy. Nevertheless, in this paper, the author attempted to supply data through clinical cases which not only illustrate improvement with this treatment but demonstrate the operation of some of the major psychodynamics of group psychotherapy.

**The New Veteran and the Future for the Practice of Medicine.** DR. CONRAD SOMMER, Chicago.

The recent wars in which this country has been engaged were followed by the development of federally controlled and staffed medical programs for the veterans of these wars. This program has been largely centered in the Veterans Administration. The present war will greatly increase the amount of medical practice of this type. The prospect is that upward of 13,000,000 persons will have a right to full hospitalization benefits, both for service-connected illnesses and for any other illness that may develop after the return of the veteran to civilian status.

There is, unfortunately, insufficient closeness of relationship between members of the general medical profession and that part of the profession found in the Veterans Administration.

Physicians, generally, and psychiatrists, in particular, should play a more dynamic role in the care of sick veterans. This enlarged medical role includes a greater use of technics available: occupational therapy, clinical psychology, vocational guidance, recreational therapy, social work and other professional services contributing to the welfare and health of sick persons. The need for fundamental and total rehabilitation of veterans arises from the two serious personality readjustments necessary in moving from civilian to war status and back from combat to peace status.

If the medical profession assumes this dynamic role in the total rehabilitation of veterans, it will gain additional prestige and authority. This may diminish the trend toward socialization of medicine.

DISCUSSION

DR. LLOYD H. ZIEGLER, Wauwatosa, Wis.: This interesting paper points to coming events. I am sure

you would be impressed by a moving picture made in England called "Psychiatry in Action." It demonstrates the methods and facilities used in a densely populated country to restore psychiatric casualties to usefulness.

Men and women have been sensitive about being considered psychiatric casualties. They will continue to be so. It is not difficult to understand why they might seek out the chaplain rather than the physician. There must be teamwork in this whole rehabilitation program, in which the physician, the minister, the business man, the manufacturer, the educator and many others will make up the team.

What is meant by rehabilitation? To me, it is freeing the patient from pain or distress and providing him with opportunities to be as useful as possible in earning a wholesome living for himself and his family. Many of these men will have spent three to five years of their lives in military service, with one or two years in active combat. Let us as physicians condition ourselves to avoid making invalids out of men who have it in them to do better.

The giving of pensions and rehabilitation are not synonymous, by any means. Congress needs much education along these lines. Everything should be done to restore the health and independence of the returning casualties so that they may not be the slaves to disease, attitudes or economic bottlenecks.

Some socialization of medicine, and of other services, may be expected. The leaders in the medical profession should guide this impending change with professional wisdom. As Dr. Sommer has pointed out, the time has come for members of the profession to give up some of their professional isolation and unite wholeheartedly with the many forces of rehabilitation all about them.

DR. M. T. KOENIG, Chicago: I, too, have had experience with the Veterans Administration for many years, and I may say that Dr. Sommer's paper was pleasant but not realistic. He speaks of various facilities for treatment, vocational training and occupational therapy. My experience with veterans of the last war was that they did not want to get well; that is a factor which must be taken into consideration. The veterans who were adequate people to start with have rehabilitated themselves very well, but the majority of those who are still on a pension of the government are men who do not want to get well.

This attitude is fostered in great measure by the various veterans' organizations and by public opinion in general. Dr. Sommer has made some recommendations which sound very good. I, too, should like to make some recommendations. I should like to see a committee investigate the vocational opportunities that were given the veterans in the last war, the cost of these vocational opportunities and the results. After the last war, many of the psychiatrists who were in charge of the various psychiatric hospitals succeeded in getting many of the veterans out of the hospitals by telling them that they could not get paid for their illness. This went on until the veterans' organizations interfered, and then began the milking of the Government. Some of the things they did were simply appalling. For instance, a man who was paid for total disability for life was at the same time employed by a veterans' organization as a liaison officer, with a full salary. I can give a number of such instances. Not only will the veterans not want to get well, but the efforts of well meaning physicians will be frustrated by quasipatriotic organizations who will shout about what terrible experiences the veterans have been through and demand large amounts of money for them. I have seen veterans with diabetes, for instance, who would not enter the hospital unless they could be admitted for a service-connected disability, and they were therefore paid, under pressure of the veterans' organization. We physicians must take into consideration these facts before we make any grandiose plans. Surely, Congress should be educated, but who will sit in Congress? Our intentions are good indeed, but we should not waste our efforts on something that might come to nothing.

DR. CHARLES F. READ, Elgin, Ill.: The paper, no doubt, is addressed to members of the medical profession at large and to psychiatrists in particular. Is it not true that the men who return from war activities will be solicitously looked after by the Veterans Administration and by physicians who are working in connection with the Veterans Facilities? Dr. Sommer is apparently trying to show what may be done by the profession at large for the men who will be looked after by the Veterans Facilities. Now, the question is this: How are members of the medical profession in general to get in touch with these men who are going to be given domiciliary care, on the least provocation.

DR. RALPH HAMILL, Chicago: I have watched the service of the Veterans Administration since World War I and have spent two to three mornings a week there for the past twenty-five years. Physicians must be realistic about this problem. They must realize that a certain number of men will be coming back who cannot be satisfied with anything. Are we psychiatrists undertaking to suggest or to state that we can handle this situation? It reminds me of the meetings of the American Psychiatric Association two or three years ago, when the discussion was under way in regard to psychiatrists getting rid of all the unfit. We are told that 30 per cent of the fellows who come back are psychiatric patients. Are we going to cure them? I wonder. I do not mean that we should not make every effort, of course, to help them; but I wonder what we shall be saying ten years from now, and whether many of our efforts will not be frustrated. Some men will want to be cured, and some will not. Some will want the money value, and some will want disability value. I am frankly skeptical of too much expectation on the part of the psychiatrist.

### Hemorrhagic Encephalopathy Following Five Day Treatment of Early Syphilis with Massive Doses of Oxophenarsine Hydrochloride (Mapharsen): Report of a Case with Recovery.

DR. G. HEILBRUNN, Manteno, Ill., and DR. N. L. HOFFENBERG, Chicago.

A survey of the literature on hemorrhagic encephalopathy occurring during or after a five day period of treatment with oxophenarsine hydrochloride (mapharsen) reveals a mortality rate of only 25 per cent from that complication, as compared with a fatality rate of 76 per cent for the same mode of administration of other arsenicals. The relative benignness of this complication is confirmed by the case of a 15 year old girl with early syphilis who exhibited typical symptoms of hemorrhagic encephalopathy on the third day after completion of a five day course of treatments, with a total of 1.2 Gm. of oxophenarsine hydrochloride. Final recovery was established nine days after the onset of the cerebral incident.

The role of the therapeutic agents employed was discussed and the use of high doses of ascorbic acid recommended.

In the search for an explanation of the affective selection of this complication, attention was drawn to the psychopathic behavior of the present patient prior to hospitalization and to findings in the literature recording nervous or mental deviations in patients who later had hemorrhagic encephalopathy. It may be tentatively conjectured that a person known to be afflicted with signs of an organic or functional neuropsychiatric disorder may be predisposed to exhibit cerebral complications under the impact of the arsenical drug.

DISCUSSION

DR. C. L. NEYMANN, Chicago: I should like to remind the members of the society of the humane rights of the much abused patient with acute syphilis. After reviewing a great deal of material, involving studies of many thousands of patients. Pusey came to the presumptive conclusion that 55 per cent of all syphilitic patients finally come to some grief as a result of their disease. These patients exhibit serious syphilitic complications years after the infection. However, 45 per cent of all syphilitic patients experience no difficulties late in life provided they are not treated. At present, medicine has entered a period of active arsenical treatment, both with and without fever, of primary and secondary syphilis. Judging from reports that have come to me *sub rosa,* it is clear that some institutions employing massive doses of arsenicals, with and without artificial fever, are abusing rather than aiding the patient with early syphilis. The mortality is too high. A death rate of 3 per cent ascribed directly to treatment of a disease for which the final prognosis may or may not be poor outrages all principles of good therapeutics.

One must bear in mind that it is possible to treat primary and secondary syphilis by means of fever and arsenicals with a minimum of danger. It is also possible to treat patients with latent syphilis in a similar manner. To accomplish this it is necessary to administer average doses of arsenicals combined with fever therapy. Most patients with primary or secondary syphilis can be cured with six artificial fever treatments and six simultaneous injections of 0.3 to 0.4 Gm. of arsphenamine. Such a series of treatments can be completed in three weeks. Why, then, turn to these extremely radical procedures? In addition, the new drug penicillin seems to be efficacious and quite harmless when properly administered. Whether this drug will also prove useful in the treatment of tertiary and post-tertiary syphilis, either in combination with fever therapy or alone, will be determined when larger quantities become generally available. The risk of overwhelming the system with arsenicals does not seem to be justified in treating a disease which is neither immediately fatal nor necessarily disabling to the patient, even after years have elapsed.

DR. J. A. LUHAN, Chicago: I recently had the opportunity to study the brain of a patient who received intensive fever treatment and chemotherapy for syphilis, with a fatal outcome. The patient was a 21 year old healthy Negro with asymptomatic neurosyphilis. He received 150 mg. of insoluble, metallic bismuth intramuscularly the day before the fever treatment, 28.5 mg. of thio-bismol intramuscularly on the morning of this treatment day and then eight hours of fever treatment, during which the rectal temperature remained between 105.6 and 106 F., and the patient received 106.2 mg. of oxophenarsine hydrochloride, in divided doses of 35.4 mg. each. Intermittent confusion developed during the fourth hour of treatment and continued thereafter. The next day impaired renal function was noted, with oliguria and appearance of albumin and granular casts in a urine of low specific gravity, and increasing azotemia. Pneumonia occurred on the ninth postoperative day, which proved refractory to the effects of penicillin and specific type XX antipneumococcus serum. The patient died on the thirteenth postoperative day. Necropsy disclosed confluent bronchopneumonia, affecting all the lobes of the right lung and the upper lobe of the left lung; parenchymatous degeneration of the myocardium; pulmonary edema; toxic changes in the liver and kidneys, and hemorrhagic encephalopathy within the brain. Kodachrome photographs of cut surfaces of coronal slices through the brain and of a cross sectional slice of the midbrain showed the presence of innumerable petechial hemorrhages, particularly throughout the white matter, most of them a fraction of a millimeter in diameter. There were few of these petechiae in the medulla and the cerebellum. A photomicrograph showing several of these petechial hemorrhages revealed ringlike hemorrhages about central areas of seminecrotic brain tissue, in the center of which remnants of capillary structure or a few polymorphonuclear cells could be seen. The central amorphous material was considerably wider than the vessel in its center. No glial proliferation was apparent in the vicinity of these ring hemorrhages. No perivascular round cell infiltrations were found in the brain, and the cerebral cortex was relatively unaffected except for staining alterations of ganglion cells consistent with toxic injury. The pathologic diagnosis of the changes in the brain was cerebral purpura, most pronounced in the white matter of the internal capsule, the midbrain and the pons, and largely sparing the cerebral cortex, the cerebellum and the medulla—a picture consistent with the vasculotoxic effects of an arsphenamine or a chemically related substance.

In this connection, I recall another case of arsphenamine encephalopathy studied at the Cook County Hospital in 1943. A Negro woman of 34, in the fifth month of pregnancy, had received many injections of neoarsphenamine, intermittently, since 1934. Several days after her last treatment convulsions developed, and she was admitted to the hospital in a state of coma. The Wassermann reaction of the spinal fluid was negative. Autopsy disclosed toxic necrosis of the liver, parenchymatous degeneration of the kidneys and bronchopneumonia of the lower lobe of the left lung. The brain revealed a state of hemorrhagic encephalopathy—cerebral purpura, with a larger focus of hemorrhagic encephalomalacia of the corpus callosum. In this case one may speculate whether a marked decrease in the concentration of *l*-ascorbic acid in the blood had not predisposed this pregnant woman to the "allergic" arsphenamine encephalopathy, since Teel, Burke and Draper (Vitamin C in Human Pregnancy and Lactation, *Am. J. Dis. Child.* **56**:1004 [Nov.] 1938) found a notable decrease in the vitamin C content of the blood in a considerable proportion of pregnant women.

It appears that a deficiency of vitamin C leads to a weakening of capillary walls and interferes with the metabolic transfer of hydrogen that depends on the oxidation-reduction system of ascorbic to dehydroascorbic acid. This second function of vitamin C reduces the toxic effect of the arsphenamines by inhibiting their oxidation and thus decreasing their toxic products of oxidation. The pathologic process in arsphenamine encephalopathy (pericapillary encephalorrhagia, as Globus and Ginsburg called it) is dependent on a pri-

mary injury to the capillary structure of the brain, which, for the foregoing reasons, we should expect to be counteracted or prevented in some measure by an adequate concentration of ascorbic acid in the blood. This, and the well documented and astute observations of Dr. Heilbrunn and Dr. Hoffenberg, suggest that every patient about to undergo intensive antisyphilitic chemotherapy be given large amounts of vitamin C and its administration be continued for a number of days after the treatment has been completed.

---

DAVID SLIGHT, M.D., *President*

*Regular Meeting, Oct. 5, 1944*

**Acute Excitement Induced by Electric Shock Therapy,** DR. VERNON L. EVANS, Aurora, Ill.

It has been rather generally thought that electric shock is a fairly harmless form of therapy and that, barring the infrequent physical accidents, the treatment will not make the patient's mental condition worse if it does not help him. However, in a series of 750 patients treated with electric shock at Mercyville Sanitarium, Aurora, Ill., many manifested acute excitement as a result of treatment and 3 died of this cause.

REPORT OF CASES

CASE 1.—A man aged 37, with a condition diagnosed as schizophrenia, simple type, had been ill for two years. The onset was with excitement and overactivity. This condition changed to retardation and uninterest. The patient was retarded, fearful and quiet on entry to the hospital. By the time he had had eleven treatments he was in a state of acute excitement, which persisted and resulted in death three days after the last treatment. Hyperpyrexia (temperature 107.4 F.) developed before death. It appears that this illness began as a catatonic excitement, which became quiescent for two years and was reactivated by the electric shock therapy.

CASE 2.—A man aged 20, with a condition diagnosed as schizophrenia, of undetermined type, had been ill for seven months. At entry the patient laughed and talked to himself and was affable and cooperative, but rather retarded and suspicious. After eleven electric shock treatments he became excited, overactive and delusional. Hyperpyrexia developed, and he died seven days after his last treatment.

CASE 3.—A woman aged 46, with a condition diagnosed as involutional melancholia with schizophrenic features, had been ill for six months. She had been depressed, had threatened suicide and had impulses to harm her husband and her child. She was pleasant and cooperative on admission. She seemed to improve after twelve electric shock treatments. Nine days after the last treatment she showed signs of excitement, and in two or three days this became acute and she expressed absurd delusions. Her excitement continued and progressed, and she died twenty-two days after her last treatment.

CASE 4.—A woman aged 38, with a condition diagnosed as paranoid schizophrenia with depressive features, had been ill for two years. She had "turned against" very close friends. She had been depressed and felt that she had not done her duty. On entry to the hospital she was quiet, cooperative, affable and anxious to please. After twelve electric shock treatments she was grateful and euphoric. A few days after the last treatment she became apprehensive and excited and spoke of dictaphones and people watching through the ventilator in her room. She became out of contact and showed marked increase of psychomotor activity. This condition persisted for many days but gradually quieted, and the patient again became affable, pleasant and cooperative. She returned home and went back to work.

*Comment.*—These patients were not apparently excited at the time electric shock therapy was started. The excitement developed during or after their course of treatment. The present practice at this institution is to suspend treatments immediately at the first signs of excitement during their course. When the excitement develops several days after the treatments have been finished, the patient is given large doses of sedatives and intensive hydrotherapy at the first signs of this reaction.

Unfortunately, permission for autopsy was not obtained in any of the 3 cases in which death occurred. Many cases of similar "fatal catatonia" in which the patients did not receive shock therapy have been described by numerous writers. When autopsies have been done, the findings have included petechial hemorrhages in the brain and hemorrhages in other areas of the body. It is my opinion that the deaths resulted from the acute excitement and "exhaustion" induced by the electric shock therapy, rather than from a direct traumatic effect of the electric current on the cerebral structures.

The apparent paradox is that electric shock therapy, which acts almost as a specific to quiet acute excitement, induced it in several cases in which it was not present or was quiescent before therapy.

DISCUSSION

DR. C. L. NEYMANN, Chicago: I was interested in this presentation because I have watched and supervised many electric shock treatments. The first question concerned with this treatment is the purpose for which it is administered. It is far too serious a procedure to be used for neuroses or mild psychoses.

The theory, which has been considered seriously as an explanation both of the reaction to electric shock treatment as such and of its success in certain cases, is simple. Perhaps it is too simple. If a person with a psychosis, either functional or organic, is knocked unconscious by a blow on the head, the psychosis will cease from the moment of the blow until the patient recovers consciousness. Now, if a patient is treated every day with electric shock therapy sufficient to produce a convulsion, a deep confusion will soon occur. Later, when he has recovered from the confusion, a retrograde amnesia becomes apparent. This is psychologically similar to the reaction to a mild cerebral concussion.

The psychologic reaction is similar when the patient is treated with insulin or metrazol. The patient in a state of remission after electric shock therapy will always have a retrograde amnesia for the time while he was under treatment. Usually this amnesia extends back several months before treatment was begun. May I be permitted to express the opinion that electric shock treatment should be given at least once a day and should be continued at least to the point at which the patient is totally disoriented for time and place?

Many patients have experienced states of excitement after electric shock therapy. Whenever a state of severe or chronic excitement occurs during the course, it is advisable to give another treatment. This can be

followed by a third, or even a fourth, treatment on the same day. Soon the excitement will cease, as a result of the confusion and amnesia, which are bound to follow.

Let me repeat that treatment of a severe psychosis should not cease until the patient is disoriented for time and place. Even beyond this, his psychic state or mentality should be reduced to a merely vegetative level. He should no longer have control of his urine or feces; he should pay no attention to his food and therefore will have to be fed with a spoon. No matter how deep or how severe the psychosis was, it is nonexistent during this state. Conversely, no matter how great the excitement, this, of necessity, will cease under continued electric shock therapy. Such treatment may even be used to advantage in place of sedation if a patient suddenly becomes violent and unmanageable. Thus, periods of extreme excitement can be overcome with ease.

DR. VERNON L. EVANS, Aurora, Ill.: I knew this paper would bring up questions I could not answer. Of course, it would have been valuable to have had autopsies, but, unfortunately, they were not obtained for any of the 3 patients who died. I know little about pathology; but from what I could read in the literature, most patients who have died of acute excitement without electric shock therapy have displayed these hemorrhagic tendencies and had hyperthermia shortly before death. Autopsy showed these hemorrhages in the brain and in other organs, but these, I gathered, were the main findings, and I think no one was able to connect them directly with the cause of death. Even though there was a mortality rate of nearly 0.5 per cent, I do not feel that this should lead one to discontinue the electric shock therapy. I feel that, while at this institution 1 patient out of 250 has died as a result of the treatment, we have saved many more patients who would have died if they had not received electric shock treatment.

**Psychiatric Problems Presented by the Inductee and the Soldier.** DR. D. M. OLKON, Chicago.

In summarizing the total effect of army life on the soldier, one cannot escape the conclusion that essential mental factors conducive to mental stability are neither acquired in the milieu nor greatly modified by training and culture. In everyday life a person may get along with faulty mental equipment. Not so, however, in time of severe crisis, such as that experienced in army life, with its inflexible discipline and hazards of war combat. Therefore, in the healthy, steadfast mental equipment of the soldier lies safety and security, and on the psychiatrist rests the responsibility of recognizing and excluding the potentially mental misfit who will handicap army efficiency in time of war and become a liability to society after the war. Moreover, experience in World War I and in the present war seems to establish that once a soldier in the service has a major mental upset the chances for his rehabilitation and return to active duty are very poor.

The presentation was discussed under the following headings: (1) the psychiatric recognition of the unstable personality at the time of induction; (2) the effect of army life on emotionality of the soldier; (3) the effect of combat on an impressionable personality; (4) forced celibacy in army life and its effect on the man in the army; (5) the cumulative effect of strict army discipline; (6) the role of fear of disabilities, disease, difficult climatic conditions, insect pests, etc., in different climes on the mental breakdown of the soldier; (7) the effect of severance of home ties and deprivation of loved ones on the mental organization of the soldier; (8) the scarcity of female companionship and its effect on army morale; (9) malingering, its recognition and evaluation in the inductee and the soldier.

Each item was briefly discussed.

Treatment of mental contingencies in war was not elaborated on. Treatment of war neuroses was discussed in greater detail in a previous publication (*Dis. Nerv. System* **5**:272-277 [Sept.] 1944). Attention was called, however, to certain useless undertakings and lengthy procedures not advantageous in army practice and treatment of war neuroses.

DISCUSSION

DR. C. L. NEYMANN, Chicago: This paper gives a good summary of the various stresses and strains which soldiers must endure in modern warfare. Dr. Olkon has also reviewed the methods to be used in treating patients of this type. I think he struck the right note when he suggested that the psychiatrist should not intrude himself into the patient's personality. This theorem has been accepted by all psychoanalysts and psychiatrists. A great deal can be accomplished by allowing the patient to discuss anything he wishes, without guiding him too rigorously. The crux of the situation may rest on his fears on entering the service, his fears during service, his stresses during service or even his stresses before he entered military life. Such stresses may, and often do, encompass his juvenile and later sexual problems. I think this subject should be a rather open field. The discussion should be directed by the patient, not by the psychiatrist. I am sure we all give our hearty approval to that attitude.

## PHILADELPHIA NEUROLOGICAL SOCIETY

GEORGE D. GAMMON, M.D., *Presiding*

*Regular Meeting, Oct. 27, 1944*

**Platybasia (Basilar Impression) Secondary to Advanced Osteitis Deformans (Paget's Disease), with Severe Neurologic Manifestations; Successful Surgical Result: Report of a Case.** DR. HENRY WYCIS.

A brief historical résumé of platybasia (basilar impression) was presented.

From the etiologic standpoint, platybasia may be primary (the result of a congenital developmental anomaly) or secondary (the result of bony softening or molding).

A case is reported of platybasia secondary to osteitis deformans, producing severe neurologic manifestations. The patient was treated successfully by high cervical laminectomy combined with suboccipital decompression.

REPORT OF CASE

Mr. R. K., aged 50, was admitted to the neurosurgical service of Temple University Hospital, Jan. 11, 1944.

The patient complained of severe bilateral occipital headaches, bilateral loss of hearing and weakness of the right arm and leg, with dragging of the latter extremity. There were numbness of the right forearm and foreleg, wobbling gait and difficulty in speech, with regurgitation of fluids through the nose. Symptoms began five years prior to admission.

*Examination.*—The general appearance in the advanced stage of osteitis deformans was striking. The short squat figure, wobbling along with bent shoulders, sunken chest and great head hanging forward, was a living illustration of Sir James Paget's delineation of the disease, in 1876. Movements of the head were limited in all directions. The pupils were equal, but reaction to light was sluggish in the right eye, due to corneal scar. The fundi were normal. Horizontal nystagmus was noted on lateral gaze in either direction. The trigeminal fields were normal for all sensory modalities. The eighth nerve deafness was greater on the right. The gag reflex was present. The tongue protruded in the midline, without tremor or atrophy. There were dysphonia and dysphagia, with nasal regurgitation of fluids.

Gait was markedly ataxic, with dragging of the right lower limb. The Babinski and Hoffmann signs were elicited on the right side, with increased tendon reflexes on this side. The right upper and lower limbs showed marked weakness. There was pronounced dysmetria and dyskinesia of the right upper limb. Hyperalgesia was noted at the level of the second cervical dermatome bilaterally; otherwise sensory disturbances were not distinct.

*Laboratory Studies.*—The findings were entirely normal except that alkaline phosphatase was elevated to 36 Bodansky units per hundred cubic centimeters of serum.

*Roentgenograms.*—A block at the foramen magnum was clearly demonstrated. Herniation of the cerebellar tonsils to the level of the upper border of the first cervical vertebra was shown.

*Operation.*—On January 18, Dr. Wycis did a suboccipital craniectomy with high cervical laminectomy.

*Postoperative Course.*—The postoperative course was little short of dramatic. There was complete relief of occipital pain and of numbness and tingling of the right arm and leg. Two weeks later the patient felt nearly normal and could walk without ataxia and dragging his leg. There was decided improvement in speech and swallowing. Six weeks later there was little, if any, neurologic abnormality except for an equivocal Babinski sign on the right side.

The author urged neurologic and roentgenographic examinations of the upper cervical portion of the spine and the region of the foramen magnum in all cases of osteitis deformans to disclose the possible presence of platybasia.

DISCUSSION

DR. TEMPLE FAY: Dr. Wycis has demonstrated a case in which decompression in the area of the foramen magnum was followed by dramatic recovery.

In my first case, reported by Dr. W. E. Chamberlain (*Yale J. Biol. & Med.* **11**:487, 1939), the condition was diagnosed by several competent neurologists in this country as multiple sclerosis, syringomyelia or progressive muscular atrophy. On operation, I found compression of the high cervical portion of the cord by a dislocated atlas, although Chamberlain erroneously reported the condition as platybasia.

Since this first case, in which a successful operation was performed five years ago, there have been 19 others in my series, which I reported, with results of operation, before the Society of Neurological Surgeons in Montreal last week. In these cases, like the early ones, symptoms similar to multiple sclerosis or amyotrophic lateral sclerosis were shown. Lesions or compression at the level of the atlas and axis was disclosed in each instance.

Many of these high cervical lesions have been overlooked, I believe, because at autopsy the brain is removed from the skull above the level of the foramen magnum and the cord is usually removed from below, without inspection of the extradural sinuses and the structures around the foramen magnum. The area of the foramen magnum itself, with its relation to the spinal cord, the atlas and the axis, is not deliberately exposed to view by the pathologist at routine autopsy. There is also the difficulty encountered by roentgenologists in visualizing this area. The usual roentgenograms taken of the head or the upper part of the spine do not clearly show the atlas-axis relationship because of the overlying shadows of the mastoid in the lateral view and of the jaw in the anteroposterior view. It is necessary, therefore, to take special stereoscopic roentgenograms, anterior, posterior and lateral, to view this area clearly, and the technic must be concerned with appropriate focal depth and elimination of the overlying and offending structures. This means use of special angles. Such a technic has been developed by Dr. W. E. Chamberlain, at Temple University Hospital; Dr. E. P. Pendergrass, at the Hospital of the University of Pennsylvania, and Dr. C. Carter Hamilton, at the Chestnut Hill Hospital.

With careful roentgenograms, one may easily pick out certain deformities which otherwise would be overlooked. Recent studies have revealed that there is an abnormal anterior displacement of the lamina of the atlas, associated with relaxation of the spinous process of the axis, so that the axis is permitted to be depressed in such a way that the anterior portion of the structure carrying the odontoid process is allowed to angulate backward into the canal. The result of this structural abnormality is that the odontoid process narrows the canal anteriorly and the lamina of the atlas acts to constrict it posteriorly. An actual hourglass appearance has been noted in several instances of so-called amyotrophic lateral sclerosis. This narrowing of the canal interferes with the free venous drainage of the epidural veins, and exploratory laminectomy has revealed not only this constriction and narrowing of the vascular channels, but, when inflammatory reactions are present, enlargement, thrombosis and dilatation of the veins, so that chronic mild compression against the medulla is produced. The pressure anteriorly against the decussation of the motor pathways by the odontoid process may cause spastic paraplegia (primary lateral sclerosis?).

The most common error in diagnosis is to call this lesion "multiple sclerosis." In my experience, two or three clinical points are helpful in making the differential diagnosis between what appears to be diffuse multiple sclerosis and focal high cervical compression of a mild but chronic nature.

There is usually wasting or loss of volume in the muscles of the neck posteriorly. Frequently a distinct change in the perception of cold sense is noted when the sensory status of the area of the trigeminal nerve or the cheek is compared (by stimulation with an ice tube) with that of the second and third cervical dermatomes, below. The use of the ice tube is superior to that of pin prick and other forms of sensory testing, because the patient can, with a fair degree of accuracy, tell the difference in sensory status between the areas in such a way that they may be clearly defined. The second and third cervical dermatomes show various degrees of impairment or hypersensitivity.

My associates and I have observed wasting and atrophy of the intrinsic muscles of the hand in cases of these high cervical lesions, although, according to the textbooks and the prevailing belief, such involvement is ascribed to lower levels of the cord, around the fifth and sixth cervical segments.

When examination reveals the aforementioned deviations from the normal, it has been our custom to order "high cervical roentgenograms," with special reference to stereoscopic visualization of the region of the atlas, axis and foramen magnum.

Although the canal may be found constricted at operation, the result of the Queckenstedt test is usually negative. In my opinion this is due to the fact that the canal is oval at this level, and, although it is compressed anteroposteriorly, there is still space for fluid to transmit pressure along the lateral aspects of the oval.

I am glad to see that Dr. Wycis has added another case to the interesting series of lesions involving this level, which have in the past been so frequently unrecognized or misdiagnosed. Dr. J. J. Keegan, of Omaha, told me recently of 2 cases of so-called multiple sclerosis in which improvement followed high cervical laminectomy, as observed in my first case.

The fact that others are also finding these lesions should stimulate review of the so-called multiple sclerosis group, since neurosurgical intervention in some instances may be of definite benefit.

DR. JOSEPH C. YASKIN: I presume that Dr. Fay does not include among his present series of 19 cases those previously reported before this society. I had the opportunity to observe some of the latter cases later, especially in the wards of the Philadelphia General Hospital. They left me with a rather unpleasant impression, but it is possible that the condition had been neglected and that it was too late for satisfactory surgical intervention.

Dr. Fay's comments regarding the need for caution in diagnosing multiple sclerosis is valid. It is bad practice to make a diagnosis of multiple sclerosis too early or on too little evidence. This is particularly true when there is total absence of involvement of cranial nerves, especially the vestibular and cerebellar pathways and the optic nerves. At best, it is well for the clinician to remember that the diagnosis of lesions in the upper cervical region is at all times very difficult.

DR. HENRY WYCIS: In anticipation of the question whether or not surgical intervention might induce sarcomatous change in bone in Paget's disease, I was informed by Dr. Lawrence W. Smith that he had never encountered such an instance. However, he stated that it was not uncommon for sarcomatous changes to occur in cases of generalized osteitis deformans.

Bruit was not audible in this patient.

I wish to thank Dr. Temple Fay for his excellent discussion of my paper. Dr. Fay has sounded a warning note, and all would profit by remembering it. One should carefully check the sensory levels at the second cervical dermatome in cases of spastic paraplegia diagnosed as multiple sclerosis.

**Acute Cortical Blindness with Recovery: Report of a Case.** DR. JOSEPH C. YASKIN and DR. EDMUND B. SPAETH.

Bilateral blindness not infrequently results from bilateral lesions of the media, retina or optic nerve. The neurologic causes of bilateral blindness include bilateral severe retinitis, papilledema, optic neuritis or bilateral optic nerve atrophy associated with infections and neoplastic or traumatic factors. Lesions in the caudolateral angles of the chiasm and the visual radiations rarely cause bilateral blindness except in the region where the calcarine areas approach the poles and lie close to each other. Even here they are relatively infrequent.

C. von Monakow (Die Lokalisation im Grosshirn und der Abbau der Funktion durch kortikale Herde, Wiesbaden, J. F. Bergmann, 1914, p. 331) reported 20 cases of total blindness due to bilateral lesions of the occipital lobe, either from vascular or from infiltrating processes. In many of these cases the disturbance first appeared as a hemiopic defect, followed by complete blindness as a result of involvement of the remaining half field by the pathologic process. Bramwell, Bolton and Robinson (*Brain* **38**:447, 1915) reported a case of blindness from bilateral lesions of the occipital lobe with retention of macular vision as distinct from panoramic vision. Mella (*J. Nerv. & Ment. Dis.* **56**:563, 1922) reported a case of thrombotic cortical amaurosis, the result of the action of methyl alcohol. Marquis (*A. Research Nerv. & Ment Dis., Proc.* **13**:558, 1932), in reviewing the literature, reported 9 cases of complete and permanent blindness, the blindness being caused by vascular lesions in 6 of these cases and by trauma in 3 cases. Two cases were reported by Hemphill (*Irish J. M. Sc.* **181**:28, 1941) in which blindness resulted from occlusion of the basilar artery. Riley, Yaskin, Riggs and Tornay (*New York State J. Med.* **43**:1619 [Sept. 1] 1943) reported 6 cases of blindness from bilateral lesions of the occipital lobes. In 4 of these the blindness was caused by vascular lesions, as verified by autopsy; in 1 case it was due to metastatic carcinoma of the stomach, and in another, to a meningioma. Hamby (*New York State J. Med.* **43**:1632 [Sept. 1] 1943) reported a case of bilateral blindness due to bilateral abscess of the occipital lobe secondary to bronchiectasis.

Cortical blindness is characterized by the absence of changes in the media, retinas or optic disks and by preservation of pupillary reflexes. In some cases central (macular) vision may be retained if the occipital poles have an additional blood supply from the branches of the middle or anterior cerebral arteries. In some cases the visual area is affected primarily by changes in the small terminal vessels. When the blindness is due to slowly developing lesions in the occipital lobes, such as neoplasms or vascular disturbances unaccompanied with other evidences of focal cerebral disease or increased intracranial pressure, the diagnosis may be difficult, and the blindness may be ascribed to psychic causes.

Most cases of cortical blindness terminate fatally by reason of the grave pathologic processes. The recovery in a case is deemed unusual enough to warrant its report.

### REPORT OF CASE

M. H., a 48 year old merchant, about the middle of March 1944, had the onset of septic sore throat with acute glomerulonephritis and hypertension. About two weeks later, evidences of a subarachnoid hemorrhage developed, and he became completely blind. The neurologic abnormalities included a rigid neck and a bilateral Kernig sign; there were no other localizing signs. The pupils were large, round and central and reacted promptly to light and consensually. The fundi showed a moderate degree of arterial hypertension, with one small hemorrhage just over the macula of the right eye. In the two weeks following the patient's admission to the hospital, he gradually recovered from the glomerulonephritis and had a satisfactory return of eyesight, without any changes in the retinas.

It was felt that this man had bilateral cortical blindness. Considering the sudden onset, the lesion was probably due to a disturbance of both posterior cerebral arteries or, more likely, of the basilar artery at its bifurcation into the two posterior cerebral arteries. In view of the spontaneous subarachnoid hemorrhage, a rupture of a small aneurysm was deemed a likely process, although emoblism could not be definitely ruled out.

DISCUSSION

DR. HENRY T. WYCIS: Did recovery begin in the macula or at the periphery?

DR. JOSEPH C. YASKIN: I am not certain, but I believe vision first returned in the central field and later extended to the peripheral field. I am reasonably sure that return for form was earlier than that for color. I should like to stress that this case was not one of hysteria and that the patient had pronounced evidences of severe nephritis and subarachnoid bleeding.

**Changes in Electrical Activity of the Cortex Due to Applications of Acetylcholine.** DR. FRANCIS M. FORSTER and DR. ROBERT H. MCCARTER.

The application of solutions of acetylcholine to the exposed cortices of cats anesthetized with dial produced a period of depression of the cortical activity, followed by cortical discharges. The depression of activity varied in degree in different experiments and extended beyond the area of application of acetylcholine, and even beyond the areas of direct neuronal connection. During the depression of electrical activity, auditory spikes recorded from the auditory receptive areas were decreased or abolished, and responses of the motor cortex to stimulation were decreased or absent.

The discharges following application of acetylcholine varied from short bursts of high voltage spikes, through prolonged bursts of high voltage fast spikes to slow waves of high voltage and some wave and spike formations. These discharges tended to remain localized, but when they spread spontaneously, did so along neuronal pathways. The spread of discharges following application of acetylcholine could be facilitated by the previous application of strychnine.

Immediately prior to and during the period of spontaneous discharge following application of acetylcholine, electrical stimulation of the motor area, auditory stimulation of the auditory receptive area and strychnine firing in any of the areas studied were followed by an acetylcholine discharge if these areas had been the site of application. Stimulation of the motor area under these conditions produced an enhanced response, and previously subliminal stimuli were effective.

From these observations, it is concluded that the application of acetylcholine to the cortex produces a period of depression of electrical activity and a refractory state of the cortex, followed by a localized electrical discharge similar to discharges recorded during clinical seizures. The acetylcholine discharges are spread, either spontaneously or by strychnine facilitation, along neuronal paths.

DISCUSSION

DR. DONALD SCOTT: The authors have shown the greatest care in their technic and preparation and they are to be complimented on the large number of controls by which they have ruled out many complicating factors. I am particularly interested in the reduction of activity that they report, because I wonder whether this might be further investigated by following the temporal spread of such reduction subsequent to the application of acetylcholine. Such a study is perhaps a "shot in the dark" and I don't know whether it would be at all suggestive. I am also interested to know more about the effect of application of acetylcholine to different areas of the cortex, and I wonder whether there was any difference between the two hemispheres which would have any bearing on my question in regard to the spread of this effect immediately following application.

DR. HENRY WYCIS: I should like to ask the authors two questions.

First, do they believe that the action of acetylcholine on the cortex is due to its muscarine-like effect or to a nicotine-like action? In small physiologic doses acetylcholine produces a parasympathomimetic effect, while in large doses it produces a nicotine-like paralysis. Might not the inactivity observed with acetylcholine be due to nicotine-like paralysis? The concentrations used by the investigators here are large, I understand as high as 50 per cent. Other investigators have applied acetylcholine to the cortex in much lower physiologic concentrations, employing as low as 0.2 to 1 per cent; with such concentrations the activity has been nil. I am sure that Dr. Forster is familiar with the work of Chatfield and Dempsey, in which 1 per cent acetylcholine applied to the cortex had absolutely no effect. During increased activity, undercutting the cortex would abolish activity.

Second, in lowering of the blood pressure there is a decrease in the cerebral blood flow. Might not the lowering of the blood pressure with the slowing circulation lead to an accumulation of carbon dioxide, which would, in turn, affect the cortical activity?

DR. GEORGE GAMMON: Is the depression of function which the authors get here related to the concentration of acetylcholine? By starting with a lower concentration, could one skip the depression phase and get stimulation? Also, do the authors consider the action of strychnine similar to the action of acetylcholine? I understand that strychnine binds cholinesterase and that perhaps the two are related.

If I understand their argument, they obtained a discharge in the cortex from acetylcholine which resembled that seen in convulsive seizures, and they therefore suggest that epileptic seizures are due to acetylcholine discharge. Is there any evidence that during such a seizure or during a seizure from electrical stimulation there is any release of acetylcholine, such as occurs from stimulating the vagus nerve supply to the heart?

DR. FRANCIS M. FORSTER: We have not as yet studied the spread of the depression of cortical activity, but we plan to direct our attention in the near future to the further investigation of this phase. We have not encountered difficulty in obtaining adequate acetylcholine responses from the cortex of the parietal or the temporal lobe or from the frontal cortex posterior to the motor area. Area 4, however, frequently produces, after application of acetylcholine, a prolonged period of sharp spikes intermixed with the cortical activity, rather than sharply demarcated bursts of spikes.

Atropinization of the animal does not affect either the period of depression of cortical activity or the subsequent acetylcholine discharges. We varied the concentration of acetylcholine used in these experiments from 1 to 50 per cent in order to determine whether the concentration of the acetylcholine itself was important in the development of the depression or the discharges. We found that the depression of activity occurred when solutions of acetylcholine too dilute to produce discharges were employed. Moreover, the concentration of acetylcholine employed did not alter either the depth or the duration of the depression. The electrical changes of the cortex produced by the application of acetylcholine do not seem to depend on the slight variations in systemic blood pressure, particularly since atropinization abolished these variations.

It does not appear likely that the action of strychnine and that of acetylcholine are entirely similar, since strychnine is said to inhibit cholinesterase, whereas one would expect acetylcholine to be taking part in the enzyme system, including cholinesterase. There is no evidence that there is any release of acetylcholine during an epileptic seizure.

# Book Reviews

**Large Scale Rorschach Techniques: A Manual for the Group Rorschach and Multiple Choice Test.** By M. R. Harrower-Erickson, Ph.D., and M. E. Steiner, M.A. Price $8.50. Pp. 420, with illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1945.

In the first part of the book the authors deal extensively with the development of the group Rorschach method, stressing its merit as a time-saving device and citing evidence from other investigators as to its value in the classification, selection and screening of maladjusted persons. Adequate directions for administration and for scoring are given, and numerous illustrations appear.

The second part of the book, in which an analysis of the findings of an experimental investigation is presented, is much less convincing, from both the statistical and the clinical viewpoint. The statistical procedure open to most serious challenge is the small and poorly selected sample of subjects used for standardization purposes, involving, as it does, a college group in which more than one half are medical students and nurses. With the individual Rorschach method, such a professional group is generally conceded to report more than the usual number of anatomic responses. The authors recognize the need for contrasting control groups and include them, although a considerable amount of overlapping appears to exist in their choices. Subjects consist of (1) unselected males, (2) patients (psychotic and psychopathic) and (3) two groups of prison inmates, composed of "sex offenders" or persons "serving terms for murder, burglary, grand larceny and forgery." The data do not suggest, however, that in the third group psychopathic personalities have been eliminated.

Little attention is given to the basic problem of reliability of the group method itself, although it appears to be fairly sensitive to variations of administrative technic. Evidence is also lacking that qualitative aspects of the individual Rorschach test principles may not have been altered radically under group conditions. Nevertheless, interpretation is based primarily on principles of the individual Rorschach method, seemingly on the assumption that the two technics reveal personality patterns which are qualitatively similar. If, as the authors suggest, their book is to serve as a "manual" for the group Rorschach method, these theoretic considerations must be met before an adequate evaluation can be made of the method itself. Their statistical tabulation of responses is of value, inasmuch as it constitutes a new and genuine contribution to the literature. To date, no such analysis of responses obtained to the Rorschach cards presented by the group method has appeared.

The multiple choice test, in its original and expanded forms, is described in the third part of the book. The procedure introduces a list of answers for each card against which a subject may check his preferences, and a key is provided for the examiner giving weights to the various responses. The claim is made that this process facilitates not only administration of the Rorschach test, but interpretation as well. Three sections of the book concern themselves with validation of the multiple choice test in terms of its effectiveness in the psychiatric differentiation of military personnel. The contributors, Lieut. Floyd O. Due (MC), U.S.N.R.; Ensign M. Erik Wright, H-V(S), U.S.N.R., and Beatrice A. Wright, Ph.D., present evidence which, although favoring the use of the multiple choice test among trained workers, acknowledges its limitations when employed by persons unskilled in Rorschach interpretation. They qualify their endorsement of the test by stating that their "blind analyses were made from the interpretative principles of the individual Rorschach combined with subjective clinical hunches" (page 214). For a test which purports to objectify and quantify the Rorschach method to a degree which makes it usable by workers untrained in Rorschach interpretation, such evidence is not convincing.

Some of the material in the section on the application of interpretative principles definitely suggests a need for further research. Clinicians experienced in the use of the individual Rorschach method will find it difficult to avoid feeling that much of qualitative significance has been sacrificed, from such statements as the following: "Organic and convulsive states are pooled in this discussion inasmuch as they are indistinguishable, interpretively, in the Multiple Choice Test" (page 231), or, "Three case records will be cited to illustrate this group, one with grand mal epilepsy and two cases demonstrating psychiatric evidences of organic intellectual impairment, one with post-traumatic encephalopathy and the other having nervous system syphilis with paresis" (page 232). From their grouping and interpretation, the contributors seem to suggest that organic damage to the brain is to be expected with convulsive disorders, a fact which has yet to be established.

Their conclusions regarding the multiple choice test in general are that "The most accurate inferences of form and degree of maladjustment are possible in the psychoneurotic sub-groups. Organic and convulsive states can be differentiated from other diagnostic categories in a large percentage of cases, but are less accurately specified within the group. Psychopathic personalities can often be recognized by their response patterns. Mental defectives show very abnormal response records, but are not accurately discriminated by this modification of the Rorschach Test" (page 239).

The fourth, and last, part of the book contains classified lists of content obtained from group record responses based on the amplified version of the multiple choice test. This material is definitely of interest, although no conclusions are drawn from group records and no comparison made with individual records taken as a group.

Throughout the entire book, administrative details and appraisal of them are handled by trained Rorschach workers, not by untrained laymen. There is evidence of considerable success with the use of the group Rorschach methods under these conditions. Much, however, remains to be done. In commenting on the book in a recent publication (Rorschach Research Exchange **9**:46-53, 1945), Dr. Marguerite Hertz summarizes its contribution rather well when she says that "'Large Scale Rorschach Techniques' is valuable as a pioneer effort," but that "it is still unsuited for widespread application." Just how far this falls short of the authors' intention is suggested by the publisher's statement on the jacket flap of the book, that the authors

. . . have devised an entirely new test which can be readily used for screening out maladjusted persons by investigation *without extensive training in the Rorschach method.* They present evidence to show that by a simple procedure, taking a few minutes to administer and to evaluate, psychiatrist, psychologist, psychiatric social workers, educator, or counselor may now avail himself of the fruits of research of many years in the Rorschach method."

Many Rorschach workers skilled in the use of the individual method will agree with Dr. Hertz when, in speaking of the group Rorschach and the multiple choice test, she further concludes: "Both tests may be used to advantage only by workers who are steeped in Rorschach methodology, who are willing to subject the tests to thorough study, and to treat their results with suspended judgment." Many will question the wisdom of attempting such oversimplication for the purpose of mass consumption and will regret that such a potentially dangerous weapon has already been placed at the disposal of the novice without proper validation.

**The Examination of Reflexes: A Simplification.** By Robert Wartenberg, M.D. Price, $2.50. Pp. 222. Chicago: The Year Book Publishers, Inc., 1945.

The primary purpose of this monograph is to simplify the technic and interpretation of reflexes. The author attempts to bring light on the confusing situation which has been produced by the placing of some investigator's name on the reflex obtained by striking a certain part of the body. In this respect he has done a good job. The only adverse criticism of the work lies in the possibility that, in the process of clarifying the situation, the author may lead some readers to believe that the testing of the reflexes is the major part of a neurologic examination. In fact, the author himself states in the preface: "Testing of reflexes and their proper evaluation undoubtedly constitute the most important part of the neurologic examination." Unfortunately, this is the impression of many physicians who are not trained in the intricacies of the anatomy and physiology of the nervous system. To the neurologist, however, the status of either the motor system or the cranial nerves, for example, is of a great deal more importance than the presence or absence of any, or all, of the reflexes. In fact, deviations in the reflexes are usually of no importance except when they are considered in conjunction with the other findings of the neurologic examination.

All of the reflexes are discussed fully, and it is shown that most of the so-called new reflexes are merely old ones elicited by some slight variation in the technic of producing an elongation of the muscle under consideration. The essentials which are necessary to an understanding of the physiology of the reflex and an interpretation of the results are clearly stated in eleven basic principles. These eleven basic principles should be known by every physician who performs a neurologic examination, and they are therefore repeated here in brief. 1. Every striated muscle is capable of contraction on reflex stimulation. The most important reflex stimulus consists of a brief concussion and stretching of the muscle tissue. 2. These muscle stretch reflexes serve as a useful protective mechanism, especially in standing and walking. 3. The strength of the reflex action of the various muscles of any person differs widely, and the strength of the reflex action of any one muscle varies greatly from one person to another. Thus, a lesion of the pyramidal tract may increase existing reflexes and bring latent reflexes to the fore. The appearance of these usually latent reflexes does not mean that the reflexes are new. 4. Since concussion of the muscle and its stretching constitute the true cause of the deep muscle reflex, it is irrelevant whether the concussion comes from the tendon, from the neighboring joint or from bone, or is obtained through mass percussion of the muscle itself. 5. Every muscle crosses one or more joints and is comparable to a tautly drawn bowstring. A muscle reflex may be elicited by tapping on the muscle itself or by stimulation of the convex side of the arch, that is, the bone. 6. Reflex contraction of the muscle can be achieved not only from either side of the bowstring but from neighboring, and even distant, points, with the bone acting as a transmitter of the mechanical insult. Reflexes can be elicited from remote places, particularly where there is functional or organic reflex hyperirritability. The use of the term "extension of the reflexogenous zones" is therefore incorrect. 7. Transmission of concussion through the bone in favorable circumstances may affect several functionally different muscles and thus evoke multiple, but completely independent, unrelated reflexes. One often elicits more than one reflex, the complexity of the response depending on the position of the limb, the strength and direction of the stroke, the relative strength of the reflexes and the degree of general reflex irritability. 8. Each of the clinically important reflexes can be elicited in normal persons in three, four, or even more, ways. A boundless confusion results in giving a special, or even a proper, name to each way of eliciting a single reflex. The chief focus of attention should be on the muscle whose action is provoked and not on the point of elicitation of the reflex. 9. Reflexes are the result of concussion and stretching of muscles, and the use of such terms as tendon, bone, periosteal, osteoperiosteal, osteotendon, joint, fascial or aponeurotic reflexes is misleading. 10. There is no justification for the use of the term "paradoxic" or "antagonistic" reflex. These phenomena are simply occasional forms of well known deep reflexes appearing under certain conditions and depending on particular technics applied in their elicitation. They are easily understandable, normal phenomena. 11. The second large group of reflexes are called superficial, or "skin," reflexes. In the superficial reflex, a stimulus applied to the skin evokes the reflexive contraction of the muscle. It is an indirect muscle reflex. Superficial reflexes differ from deep reflexes in that they are evoked by a greater variety of stimuli; their zone of excitation is much more extended; their latent period is longer, and their fatigability is greater. Whereas every muscle has its deep muscle reflex, only a few muscles have their superficial reflexes as well.

**The Story of a Hospital.** By Charles A. Elsberg, M.D. Price, $3.50. Pp. 174. Paul B. Hoeber, Inc., 1945.

Dr. Elsberg has given an accurate account of the development of the Neurological Institute. He carries one fluently and with easy motion through the tumultuous vicissitudes of its early years: that period of crystallization and growth of the organization which has attained a place of distinction in the medical annals of New York.

He describes with simple clarity the labor and devotion of the founders, both lay and medical, and tells how the indomitable energy of two medical men by procuring funds galvanized the board of directors into securing the incorporation, the purchase of the old building and the organization of the hospital as an entity.

One could wish he had drawn a more graphic picture of those early days, with more details of the inevitable clash of strong dominant personalities, the confusion of the clinic afternoons, when the traffic lines of patients bound for the physical therapy department became jammed with the lines of clinic patients going to be examined, and the ease with which this tangle was always rectified by one small, calm, efficient nurse. A striking picture of the line of applicants waiting for admission to the outpatient department, which often reached more than halfway down the block, might have been added, as well as a mention of the flexibility of the administration, whose ingenuity in wangling additional space for the expanding activities of new departments seemed unbounded. To those of us who participated in this period, these details form a pleasing section of a mosaic that is an integral part of the early history of the Institute.

The story of the reorganization which resulted in a new building and coalition with the Columbia-Presbyterian Center is well told, although the author is somewhat modest about the part he played in this development.

The account of the final amalgamation with the Presbyterian Hospital and the subsequent reorganization signalizes another milestone in the progress of the Institute and contains illuminating details of the changes in the various departments and the closer coordination with the staff of the Presbyterian Hospital. The closing chapter takes cognizance of the fact that the Institute is weathering a second world war, which, while absorbing many of its staff for the armed forces, has not stripped it to the bone, as was the case in World War I.

Dr. Elsberg in the closing chapter yields to the temptation to philosophize in his gentle way on the cataclysmic throes of the world today. He takes issue with the pessimistic views of Bertrand Russell concerning the future of mankind and gives in outline an ethical formula for the establishment of a lasting peace.

**The Cultural Background of Personality.** By Ralph Linton, Ph.D., Professor of Anthropology, Columbia University. Price, $1.50. Pp. 153. New York: D. Appleton-Century Company, Inc., 1945.

This book was written as an outgrowth of a series of lectures delivered by the author on the general subject of the interrelations of culture, society and the individual. Dr. Linton recognizes the necessity for the collaboration and utilization of many technics in the study of personality. He seeks the cooperation of psychology, sociology and anthropology. He should have included also anatomy and physiology.

In this small book are packed a wealth of information and an honest appraisal of what has been accomplished in the field of personality by the social sciences to date. The psychiatrist can read with profit the general concepts of the anthropologist. What is more, there appears a discussion of the shortcomings as well as the advantages of the anthropologic technic.

The chapters on the concept of culture and the one on personality are particularly good. The organization and classification of material provide in condensed form a quick orientation for the reader and give him a point of view which stresses the all-pervading factor of society, of culture, of environment on personality evaluation. For example, the author redefines neurosis as "an individual value-attitude system not shared by other members of society" which the individual expresses "in specific overt responses not adjusted to his cultural and social milieu." He agrees that the first few years of life are crucial for the establishment of the highly generalized value-attitude systems which form the deeper levels of personality content.

Dr. Linton concludes that culture is the main factor producing "normal" personality in any group. However, he states that the causes of aberrant personality are still imperfectly understood.

This book is highly recommended.

# News and Comment

## AMERICAN SOCIOMETRIC ASSOCIATION

An American Sociometric Association has been founded, and its first officers were elected by means of a sociometric poll. Officers of the association are: president, J. L. Moreno; secretary, Helen H. Jennings; treasurer, George A. Lundberg; counselors, Gardner Murphy, Ronald Lippitt and Zerka Toeman.

The association has at this time 100 charter members and 175 new applicants for membership. The aim of the association is to provide a meeting point for the various social science associations as a center in which their mutual research interests can be promoted. Its charter membership consists of a cross section of sociologists, psychiatrists, psychologists, anthropologists, social workers and so forth.

Annual membership fee is $5, including subscription to the journal *Sociometry*. Communications and applications for membership may be addressed to: American Sociometric Association, Room 327, 101 Park Avenue, New York 17.

## AMERICAN PSYCHIATRIC ASSOCIATION

The American Psychiatric Association is desirous of being of service to its members and to other physicians interested in psychiatry. The association is particularly interested in making available "refresher courses" of about three months and fellowships or residencies of a year or more. In order that appropriate plans may be made, it is urgently requested that physicians now in the armed forces who wish to avail themselves of such opportunities communicate with the secretary, Dr. Winfred Overholser, Saint Elizabeths Hospital, Washington 20, D. C., indicating their desires.

## CORRECTION

In the article by Dr. Silvano Arieti entitled "Primitive Habits and Perceptual Alterations in the Terminal Stage of Schizophrenia," in the May issue (ARCH. NEUROL. & PSYCHIAT. **53**:378, 1945), second column, page 381, the last word in the third from the last line of the first paragraph should be "lobotomy" instead of "lobectomy."

Archives of Neurology and Psychiatry

VOLUME 54 AUGUST 1945 NUMBER 2



# PROGRESSIVE FACIAL HEMIATROPHY

ROBERT WARTENBERG, M.D.

SAN FRANCISCO

An intense and widespread interest has been manifested in the disease described by Parry, in 1825, and by Romberg, in 1846, and named by Eulenburg, in 1871, progressive facial hemiatrophy. In recent years many articles have appeared on this subject in English, German and French. Among these the monographic work of Archambault and Fromm [1] is outstanding. Not only the neurologist but the internist, the pediatrician, the dermatologist, the surgeon, the ophthalmologist and the cosmetologist have contributed to the literature on this subject. This fact is the more remarkable since progressive facial hemiatrophy hardly presents diagnostic or therapeutic problems of magnitude. It is rather the great variety of clinical features and the pathogenesis of this puzzling disease that have attracted such widespread attention. From this standpoint the following clinical observations are noteworthy.

## REPORT OF CASES

CASE 1 (National Hospital Queen Square, London, service of the late S. A. K. Wilson).—The patient was a 20 year old girl. Her complaints were: wasting of the right side of the face since the age of 7 years; fits since the age of 15; general headache and knifelike pains through the right side of the head for four or five years, and recent weakness of the whole left side. When she was 4 years old, a "white spot" was noticed on the right side of her forehead, near the midline. This spot gradually spread upward to the scalp, which became completely bald in that area. When she was 7 years old, it was noticed that the right side of the head sank in; for the four years prior to her admission to the hospital this depression had remained stationary. At the age of 7 she had for the first time a sudden attack of a tight feeling spreading up from the left thumb to the shoulder, the face and down the leg, the left foot being affected last. There was no loss of consciousness. This was followed by pain down the whole left side of the body and by muscular twitchings; sometimes the drawing up started in the toes of the left foot and worked into the left arm and the left side of the face. These attacks occurred once in three or four weeks; each of them left her with weakness of the left side, especially of the left arm, which would abate in one or two days. For hours after an attack her left thumb would turn into the palm of the hand. These attacks ceased one year before her admission. Five years prior to admission the diagnosis of scleroderma was made. The left side was becoming increasingly and permanently weaker. Besides these attacks, she had in the previous three years four severe attacks, which started with a sick feeling in the stomach and giddiness. She had general convulsions and frothing at the mouth and became unconscious; she bit her tongue and was incontinent.

Fig. 1 (case 1).—Right-sided progressive facial hemiatrophy with jacksonian sensory and motor epilepsy on the left side.

Examination revealed pronounced atrophy on the right side of her face, affecting especially the subcutaneous tissues and bone, most noticeably over the forehead (*fig. 1*). Here there was a furrow to the right of the midline, extending 7.5 cm. back from the hair line. Above the hair line the furrow was completely

To the memory of Samuel Alexander Kinnier Wilson, who suggested this publication.

From the Department of Neurology, Division of Medicine, University of California Medical School.

1. Archambault, L., and Fromm, N. K.: Progressive Facial Hemiatrophy, Arch. Neurol. & Psychiat. **27**:529 (March) 1932.

hairless and covered with yellowish brown scales. The skin over the furrow was paper thin, appeared darker, was glossy, showed fine wrinkling and was attached to the bone. Fine subcutaneous vessels were visible in the area of the furrow. The atrophy on the medial edge of the furrow was greater than on the lateral edge. The furrow continued down the right side of the face to the tip of the nose. The atrophy tapered downward. The upper lip was thinner on the right side than on the left. The skin on the right cheek was normal. The iris of the right eye was darker than that of the left eye. Otherwise there were no motor, sensory or vasomotor disturbances; the muscles were not involved. Electric irritability of the muscles was essentially normal. The cranial nerves were normal. The grip of the left hand was weaker than that of the right. The brachioradial and the triceps reflex were stronger on the left than on the right. There was associated movement of the thumb on bending of the fingers of the left hand; none appeared on the right. Abdominal skin reflexes were weaker on the left side than on the right.

*Summary.* — Pronounced right-sided facial hemiatrophy was present in a 20 year old girl, with sensory and motor jacksonian epilepsy on the left side, generalized epileptic attacks and mild signs of spastic paralysis on the left side.

CASE 2.—This case was described in detail in a previous paper.[2] A 19 year old rancher had noticed at the age of 10 years thinning of his hair on the right side of his head, beginning in front and creeping backward. At the age of 14, when the bald spot was already conspicuous, it was noticed that the right cheek had become thinner. Four years prior to his admission a diagnosis of tuberculous uveitis of the right eye was made. For a year he had been having attacks of twitching, which first were limited to the third, fourth and fifth fingers of his left hand. Later, this twitching spread to the left forearm and then to the left arm. Such attacks were occasionally followed by loss of consciousness and by incontinence of urine. In the last half-year the twitching in the third to fifth finger and in the left forearm became nearly constant. More violent attacks occurred three or four times a week, with twitching of the whole left arm.

Examination revealed that he had no complaints other than twitching of the left arm. There was pronounced hemiatrophy of the right side of the face. The skin showed no essential changes. Atrophy involved only the subcutaneous tissues and bone. There were pigment spots on the right side of the neck. There was partial alopecia involving the right side of the head and the right eyebrow medially. The right ear was normal. The muscles were not affected. There were no vasomotor disturbances. The temperature of the skin, as well as its reaction to mechanical stimuli, was the same on both sides. Histologic examination of specimens of the skin and bone taken on trepanation over the area of the alopecia revealed no essential changes. Ophthalmologic examination revealed remnants of tuberculous uveitis on the right side. The cranial nerves were normal. There was a slight increase of the deep reflexes of the left arm; sensibility was normal. There were constant fine twitchings of the fourth and fifth fingers, which spread to the flexors of the hand and at times to the flexors of the forearm. Attacks of violent tonic and clonic twitchings of the left arm, lasting one and a half minutes and not accompanied with loss of consciousness, occurred fifteen times or more a day. These attacks varied in intensity and occasionally culminated in grand mal attacks, with loss of consciousness, general convulsions, incontinence and ensuing deep sleep.

During the three weeks' observation in the hospital the number of attacks increased; the small ones occurred from sixty to seventy times a day and resisted all therapy. The surgical procedure, namely, extirpation of the primary cortical cramp center from which, on electric stimulation, flexion of the fourth and fifth fingers could be elicited, brought the attacks to a stop, and the patient was able to return to work.

In the nine months which followed this operation he experienced seven attacks, with twitching of the left shoulder. Examination ten years later revealed that the hemiatrophy had remained stationary. The patient had regained good strength in the left hand but was awkward in fine finger movements. The attacks had ceased.

*Summary.*—Right-sided progressive facial hemiatrophy occurred in a 19 year old boy, starting at the age of 10. He had had jacksonian epilepsy for one year prior to observation; it had begun in the fingers of the left hand and was of the character of epilepsia partialis continua of Kojevnikoff.

CASE 3 (University of California Hospital, neurosurgical service of Dr. H. C. Naffziger).—A man aged 23 had been operated on at the age of 11 years for an undescended right testicle. He had been having general epileptic attacks since the age of 6 years. These attacks had never offered any localizing clue. When the patient was about 7 years of age, his parents noticed retardation in the growth of the right side of his face; this did not cause the slightest discomfort. The progress, which was very slow, ceased two or three years prior to his admission to the hospital.

The patient showed very pronounced atrophy of the right side of the face, with loss of hair on the skull in exactly the same area as in cases 1 and 2 (fig. 2). There was further loss of hair on the medial third of the right eyebrow. The ear was not involved. The skin was somewhat thinned over the affected area but was otherwise essentially normal. There was slight atrophy of the right side of the tongue. The right pectoralis major muscle was smaller than the left. The testis and the epididymis on the right side were about one-half to one-third the size of those on the left. The deep reflexes on the left were somewhat more active than those on the right. No pathologic reflexes were demonstrable. Roentgenograms showed that the entire right half of the cranium was less developed than the left.

CASE 4.—A woman 26 years of age stated that when she was 3 years old it was noticed that her left cheek "went in." The indentation increased very slowly until two years prior to examination, when progress ceased. The patient had no discomfort. She showed very pronounced left-sided facial hemiatrophy, without involvement of the hair or skin (fig. 3). The subcutaneous vessels on the forehead were visible through the skin, which showed some discoloration but no definite pathologic changes. On the left side of the face the muscles supplied by the facial nerve and the masseter muscle showed some atrophy but no functional impairment.

2. Wartenberg, R.: Zur Klinik und Pathogenese der Hemiatrophia faciei progressiva, Arch. f. Psychiat. [illegible]:602, 1925.

Fig. 2 (case 3).—Right-sided progressive facial hemiatrophy with general epileptic attacks.

Fig. 3 (case 4).—Left-sided progressive facial hemiatrophy without involvement of the hair or skin.

CASE 5.—Left-sided facial hemiatrophy of very slow progression was slightly corrected by plastic operation. The hair, muscles and skin were not involved; only the homolateral half of the tongue showed marked atrophy (fig. 4).

CASE 6.—A 33 year old housewife noticed, twelve years prior to examination, a small dent on the right side of the forehead, 1 fingerbreadth lateral to the midline. The indentation increased in depth and spread upward very slowly. Five or six years prior to examination she noticed an indentation in her right cheek, which since then has slowly increased in depth. She has never felt any discomfort relative to her face. The atrophy was more marked over the forehead and on the medial edge of the area involved than on the lateral edge (fig. 5). The fat of the cheek had diminished strikingly. The skin and muscles were not affected. There was dandruff on the right side of the scalp but none on the left. There were no disturbances of the sympathetic nervous system, and the fifth nerve was normal. Roentgenographic examination showed normal bones. The right eye exhibited no signs of infection, but there were more and larger vessels around the limbus of the right eye than around that of the left eye. On examination with the slit lamp the capillaries of the right eye were found to be larger than those of the left.

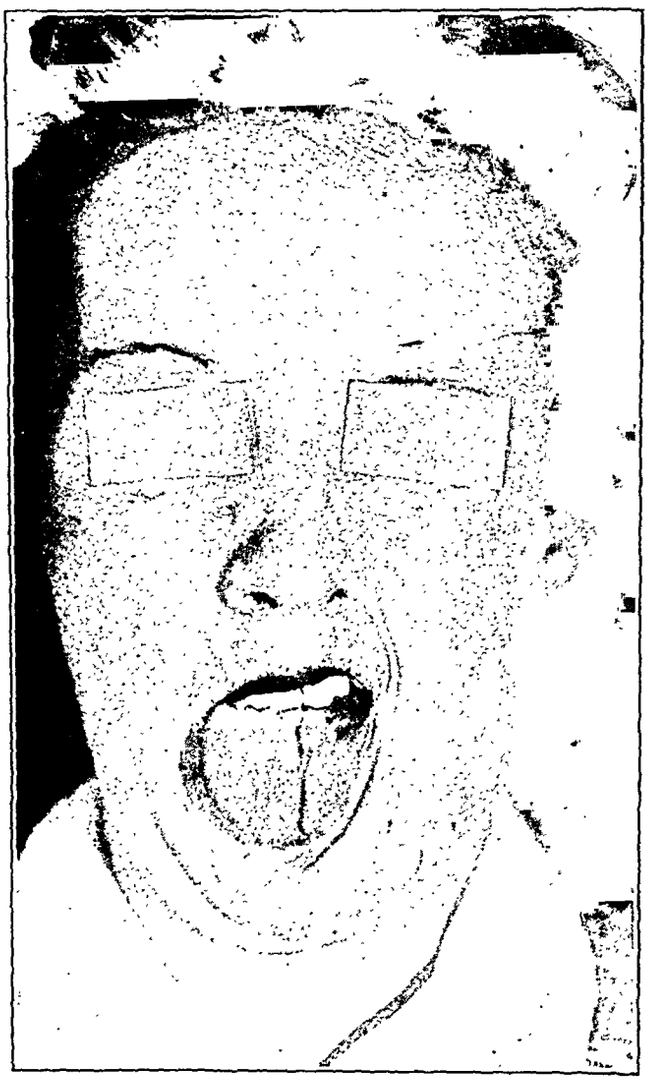


Fig. 4 (case 5).—Left-sided progressive facial hemiatrophy with pronounced homolateral atrophy of the tongue.

*Summary.*—Right-sided facial hemiatrophy has produced in the course of twelve years only

mild changes in the fat and subcutaneous tissues, leaving the skin intact.

CASE 7.—A 27 year old housewife had noticed very slow shrinking of the right cheek, which had started about nine years ago. The cheek itched occasionally; otherwise there were no complaints. There was slight atrophy of the skin and subcutaneous tissues above and outside the angle of the mouth on the right side in an area 2 by 1 cm. (fig. 6). The skin in this area was brown, atrophic and crinkled. The fat pad on the right cheek was diminished distinctly. On the right side of the forehead, 1 fingerbreadth from the midline above the right eyebrow, there was a fine streak where the skin was shiny, slightly atrophic and crinkled. This area was about ⅓ finger length and ½ fingerbreadth. The cranial nerves and the cervical sympathetic trunk were normal.

*Summary.*—In the course of nine years, right-sided facial hemiatrophy has produced only mild changes in the skin of the forehead and slight changes in the skin and subcutaneous tissues of the corner of the mouth.

Fig. 5 (case 6).—Right-sided progressive facial hemiatrophy of twelve years' duration with mild symptoms.

## INVOLVEMENT OF HAIR IN FACIAL HEMIATROPHY

Involvement of the hair of the scalp was a striking feature in the first 3 cases presented here. The affected side showed circumscribed complete alopecia. Alopecia of similar location and extent has been reported in some published cases. Mention may be made of the cases of Cords,[3] Dana,[4] Harris,[5] Klingmann,[6] Lloyd,[7] Montanaro and Pierini,[8] Osborne[9] and Tauber and Goldman.[10] Involvement of the hair in the form of alopecia or of canities (*blanching*) was mentioned by Bernstein,[11] Bory,[12] Diller,[13] Jendrassik,[14] Joss-

Fig. 6 (case 7).—Right-sided progressive facial hemiatrophy of nine years' duration, with only mild involvement of the skin of the forehead and cheek.

3. Cords, R.: Strichförmige Gesichtsatrophie und Auge, Ber. d. deutsch. ophth. Gesellsch **47**:53, 1928.

4. Dana, C. L.: Textbook of Nervous Diseases, ed. 10, New York, William Wood & Company, 1925, p. 606.

5. Harris, W.: *Neuritis and Neuralgia*, New York, Oxford University Press, 1926, pp. 243 and 283.

6 Klingmann, T.: Facial Hemiatrophy, J. A. M. A. **49**:1888 (Dec. 7) 1907.

7. Lloyd, J. H.: Hemifacial Atrophy, M. News, Philadelphia **67**:604, 1895.

8 Montanaro, J. C., and Pierini, L. E.: Hemiatrofia facial progresiva, Semana méd. **1**:704, 1938.

9. Osborne, E. D.: Morphea Associated with Hemiatrophy of the Face, Arch. Dermat. & Syph. **6**:27 (July) 1922.

10. Tauber, E. B., and Goldman, L.: Hemiatrophia Faciei Progressiva, Arch. Dermat. & Syph. **39**:696 (April) 1939.

11. Bernstein, E.: Hemiatrophia alternans facialis progressiva mit halbseitiger Alopezia, Pigmentverschiebung und Hautatrophie, Dermat. Wchnschr. **90**:235, 1930.

*(Footnotes continued on next page)*

mann,[15] Lauber,[16] Léri,[17] Loewy-Hattendorf,[18] Meyer,[19] Ratner,[20] Stief and Tanka,[21] Stiefler,[22] Vassilevski,[23] Vivado,[24] Mailhouse [25] and others. When half of the lip is affected, it may become completely hairless, whereas the mustache grows naturally on the healthy side (Blumenau [26]). Also, the eyelashes and the hair of the eyebrow on the affected side may be more or less absent. Bernstein [11] reported a case of progressive facial hemiatrophy with "unilateral alopecia," so conspicuous was the loss of hair.

In the course of progressive facial hemiatrophy, the hair of the scalp and face is involved not only frequently but very early. This involvement of the hair may precede the appearance of any other sign of the disease, as shown in cases 1 and 2. In the older literature many cases were reported in which falling out or blanching of the hair was the initial manifestation. From pertinent cases published recently, reference may be made to the cases of Cheever,[27] Jossmann,[15] Archambault and Fromm [1] (case 3) and Wolfe and Weber.[28]

12. Bory, M. L.: Un cas d'hémiatrophie faciale progressive avec sclérodermie partielle du cuir chevelu, Bull. Soc. franç. de dermat. et syph. **36**:863, 1929.

13. Diller, T.: A Case Exhibiting Symptoms of Facial Hemiatrophy and Jacksonian Sensory Epilepsy, J. Nerv. & Ment. Dis. **20**:284, 1895.

14. Jendrassik, E.: Ueber die Hemiatrophia faciei, Deutsches Arch. f. klin. Med. **59**:222, 1897.

15. Jossmann: Hemiatrophia faciei, Zentralbl. f. d. ges. Neurol. u. Psychiat. **55**:348, 1930.

16. Lauber, H.: Ein Fall von Hemiatrophia facialis progressiva, Ztschr. f. Augenh. **57**:492, 1925.

17. Léri, A.: Hémiatrophie faciale avec paralysies multiples des nerfs crâniens, Bull. et mém. Soc. méd. d. hôp. de Paris **37**:1594, 1921.

18. Loewy-Hattendorf, E.: Demonstration, Zentralbl. f. d. ges. Neurol. u. Psychiat. **27**:413, 1922.

19. Meyer, H. E.: Ueber Hemiatrophia faciei und totalis, Med. Klin. **32**:352, 1936.

20. Ratner, T.: Ueber einen Fall von Hemiatrophia cruciata progressiva, Deutsche Ztschr. f. Nervenh. **97**: 304, 1927.

21. Stief, S., and Tanka, D.: Rare Case of Hemiatrophia Faciei, Orvosi hetil. **69**:459, 1925; abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **41**:649, 1925.

22. Stiefler, G.: Ueber die Hemiatrophia faciei progressiva bilateralis, Jahrb. f. Psychiat. u. Neurol. **51**: 277, 1934.

23. Vassilevski, M.: A Case of Progressive Hemiatrophy of the Face, Shoulder Girdle and Hand, Sovet. nevropat. **2**:78, 1933.

24. Vivado: Sobre un caso de hemiatrofia de origen simpatico, Rev. méd. de Chile **56**:1066, 1928.

25. Mailhouse, M.: Facial Hemiatrophy, J. Nerv. & Ment. Dis. **28**:225, 1901.

26. Blumenau, L.: Unilateral Atrophy of the Face, Vestnik psikhiat. i nevropat. **7** (pt 1):219, 1889-1890; abstracted, J. Nerv. & Ment. Dis. **15**:259, 1890.

27. Cheever, A. W.: A Case for Diagnosis (Congenital Syphilis? Hemiatrophy?), Arch. Dermat. & Syph. **34**:297 (Aug.) 1936.

28. Wolfe, M. C., and Weber, M. L.: Progressive Facial Hemiatrophy, J. Nerv. & Ment. Dis. **91**:595, 1940.

The fact that alopecia may precede the atrophy is diagnostically important, since for this reason progressive facial hemiatrophy must be considered as a possible cause of obscure circumscribed alopecia. Thus, the statement of Oppenheim [29] that the hair of the head is almost never affected in cases of hemiatrophy is untenable.

The location of the alopecia and canities on the skull and on the face is remarkable. The involvement of the hair does not extend to the midline but occupies an area which is best called the "paramedian area." This area consists of a strip about 2 fingerbreadths in width, lateral and parallel to the midline, over the forehead and the whole face, involving the inner aspect of the eyebrow, the eyelashes and the outer part of the mouth. The atrophy is most pronounced on the medial edge of this strip. Numerous pictures and descriptions of facial hemiatrophy show again and again the localization of alopecia, canities and the atrophic process, as seen in the first 3 cases reported here. Reference may be made to cases of Nikitin,[30] Flint,[31] Romberg,[32] Leskowski [33] and Bramwell.[34] Some authors emphasize that the atrophy does not reach the midline but stops at a distance of 1 or 2 fingerbreadths from it. Therefore, the statement of Curschmann [35] that the atrophic process always ends exactly in the midline is hardly tenable. Neither is it correct to speak of "the usual strictly midline delimitation of the lesion from the normal side" (Cox and Maclure [36]).

Not only is the atrophy most pronounced in the paramedian area, but the atrophic process usually starts there—at the outer part of the mouth, the inner part of the eye and on the forehead, lateral to the midline (Archambault and Fromm,[1] Diller,[13] Jendrassik [14] and Walsh [37]).

29. Oppenheim, H.: Lehrbuch der Nervenkrankheiten, ed. 7, Berlin, S. Karger, 1923, p. 2167.

30. Nikitin, M. P.: Case of Atrophy in the Area of the First Branch of the Trigeminal Nerve, Obozr. psikhiat., nevrol. **15**:70, 1910.

31. Flint, G.: Case of Partial Atrophy of Right Side of Face, Tr. Ophth. Soc. U. Kingdom **52**:308, 1932.

32. Romberg: Klinische Ergebnisse, Berlin, A. Förstner, 1846, p. 75.

33. Leskowski: Hemiatrophia facialis, Neurol. Centralbl. **25**:1008, 1906.

34. Bramwell, B.: Atlas of Clinical Medicine, Edinburgh, T. & A. Constable, 1891, p. 97.

35. Curschmann, in von Bergmann, G., and Staehelin, R.: Handbuch der inneren Medizin, ed. 2, Berlin, Julius Springer, 1926, vol. 5, pt. 2, p. 1482.

36. Cox, L. B., and Maclure, A. F.: Facial Hemiatrophy, Australian & New Zealand J. Surg. **5**:68, 1935.

37. Walsh, F. B.: Facial Hemiatrophy, Am. J. Ophth. **22**:1, 1939.

ABORTIVE FACIAL HEMIATROPHY

The fact that the pathologic changes associated with hemiatrophy are found mostly in the paramedian area is of diagnostic importance, since thereby early stages of the disease and the condition to be designated as "abortive progressive facial hemiatrophy" may be recognized. The term "progressive" must not be taken literally. The atrophy does not progress indefinitely, and the final stage never is a complete atrophy of the tissues. The disease progresses for a number of years and then becomes stationary for the remainder of life. The development of progressive facial hemiatrophy may thus cease at any point at any time. The case of Kahler [38] might be mentioned in which the atrophy had developed in the tenth year of life and had not shown any progression at the fifty-fourth year. In some of these cases of arrested progression the process remained limited essentially to the forehead (Lloyd,[7] Bini [39]). In discussing a case in which the differential diagnosis of scleroderma and progressive hemiatrophy had been made, Pick [10] rejected the latter diagnosis because the disease had shown no progression for twenty-seven years. Such reasoning is not correct since the existence of progressive facial hemiatrophy with arrested progression must be assumed. In many cases of this type the visible changes may be so mild and inconspicuous that they escape notice on the part of the patient or, if noticed, are disregarded. The changes are to be found in such cases in the paramedian area, in the same location in which the pronounced alopecia and atrophy are seen in cases of the fully developed disease.

It is justifiable to assume that cases 6 and 7, previously described, also belong here. There is, of course, no such sharply defined entity as abortive progressive facial hemiatrophy. The illustrations clearly demonstrate the numerous transitional forms of facial hemiatrophy and show the wide range of clinical symptoms of the disease.

CASE 8.—A man 71 years of age noticed about nineteen years ago a dimple on the forehead at the hair line, 1 fingerbreadth to the right of the midline. This dimple slowly developed downward to the eyebrow. About ten years prior to examination he noticed on the forehead, and parallel to this line, another dimple, 1 fingerbreadth lateralward and not so deep. The development had been very slow. The condition had been stationary for the past six or seven years. The illustration (fig. 7) shows very slight atrophy of the subcutaneous tissue on the forehead, exactly in the area grossly affected in the first 3 cases of fully developed facial hemiatrophy. The skin was normal, and roentgenograms of the skull showed that the bones were normal.

Fig. 7 (case 8).—Right-sided abortive progressive facial hemiatrophy of nineteen years' duration, with mild manifestations on the forehead only.

CASE 9.—A 24 year old rancher had noticed seven years previously a dimple in the forehead, to the right of the midline; it had slowly progressed until the last three or four years, when it became stationary. Figure 8 shows a cleft in the forehead, directly to

Fig. 8 (case 9).—Right-sided abortive progressive facial hemiatrophy of seven years' duration, with manifestations on the forehead.

38. Kahler, O.: Ein Fall von beschrankter neurotischer Atrophie im Gesichte, Prag. med. Wchnschr. **6**:53, 1881.

39. Bini, L.: Sull' emiatrofia facciale progressiva, Riv. sper. di freniat. **61**:19, 1937.

40. Pick, W.: Sclerodermie en coup de sabre mit osteoporotischer Zone im Stirnbein oder Hemiatrophia faciei? Arch. f. Dermat. u. Syph. **167**:543, 1933.

the right of the midline. On palpation the cleft appeared deep, but with no apparent involvement of the bone. The skin over this area was adherent to the underlying tissues. It did not show any definite changes. No roentgenograms were made. The atrophic process in this case was nearer the midline than in the other cases.

CASE 10.—A housewife 47 years of age came to the clinic because of functional nervous disturbances; she did not mention the condition of her skin. On inquiry, she revealed that twenty years previously the medial side of the right eyebrow showed gradually increasing sparseness of the hair. This condition had remained stationary during the past three years. Examination of the glabella (fig. 9) showed normal hair, which extended as far as 0.5 cm. to the right of the midline. From here, the right eyebrow showed complete loss of hair to the middle, with no changes in the skin. The medial portion of the eyelashes of the right eye was completely absent. Otherwise the lid was normal. The hair on the upper lip showed no difference between the right and the left side. There were two nevi pilosi, one on the chin and the other on the front of the neck, ½ fingerbreadth above the sternum. Both were at the same distance from the midline—about 0.5 cm. to the right.

Examination of the scalp showed a completely hairless area on the top of the head; this was 4 cm. long and 1 cm. wide, starting 0.5 cm. to the right of the midline (fig. 10). Here the skin was atrophic, thin as paper and crinkled. On palpation there was a definite indentation in this area. Sebaceous glands were present. Separated from this spot, in front of and lateral to it, was another hairless area, as the illustration shows. The patient was completely unaware of her bald spots.

Fig. 9 (case 10).—Right-sided abortive progressive facial hemiatrophy of twenty years' duration, showing changes in one eyebrow. Two nevi pilosi are present on the side of the hemiatrophy in the paramedian area.

There is hardly any doubt that cases such as 8, 9 and 10 are classified best as instances of abortive facial hemiatrophy.

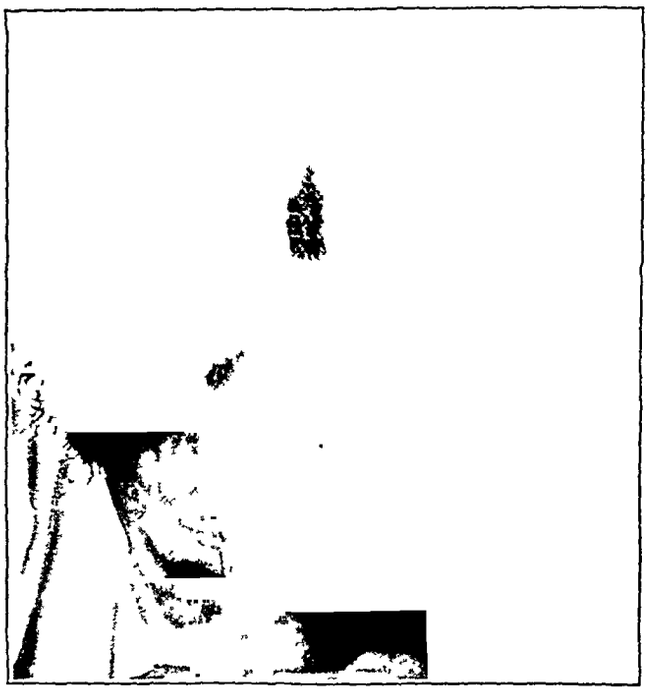


Fig. 10 (case 10).—Right-sided abortive progressive facial hemiatrophy, showing changes of the hair on the skull.

## PROGRESSIVE FACIAL HEMIATROPHY AND SCLERODERMA

In the literature (reviewed by Möbius,[41] Marburg,[42] Lauerbach[43] and Wohning[44]) the intimate connection of hemiatrophy and scleroderma has been much discussed. Cassirer[45] expressed the opinion that facial hemiatrophy was a definite form of scleroderma with special localization, as did Chasanow[46] and Archambault and Fromm.[1] Kroll[47] emphasized that a differential diagnosis between facial hemiatrophy and scleroderma may be impossible. When scleroderma is located in the face, it is called morphea, or scleroderma *en coup de sabre*. This expression

41. Möbius, P. J.: Der umschriebene Gesichtsschwund, Vienna, A. Hölder, 1895.

42. Marburg, O.: Die Hemiatrophia facialis progressiva, Vienna, A. Hölder, 1912.

43. Lauerbach, F.: Ein Fall von Hemi-Hypoplasie des Gesichtes und der Zunge, mit kritischen Bemerkungen zum Symptomenbild der Rombergschen Hemiatrophia faciei, Arch. f. Dermat. u. Syph. **144**:285, 1923.

44. Wohning, M.: Hemiatrophia faciei und Sklerodermie, Inaug. Dissert., Freiburg i. Br., N. D.

45. Cassirer, R.: Die vasomotorisch-trophischen Neurosen, Berlin, S. Karger, 1912.

46. Chasanow, M.: Beiträge zur Aetiologie der Hemiatrophie des Gesichtes, Ztschr. f. d. ges. Neurol. u. Psychiat. **140**:473, 1932.

47. Kroll: Die neuropathologischen Syndrome, Berlin, Julius Springer, 1929.

is highly appropriate, since the patient looks as if he had received a stroke over his forehead with a sword. The title of an article by Pick,[40] "Scleroderma *en coup de sabre* with Osteoporotic Zone in the Frontal Lobe, or Facial Hemiatrophy?" illustrates the difficulty in differentiating between these two conditions. In case 1 of this series, the condition, first diagnosed as scleroderma, developed into classic hemiatrophy. According to some authors (Ben,[48] Bory,[12] Osborne[9] and Truffi[49]), hemiatrophy and scleroderma may occur simultaneously in the face of the same patient, or local scleroderma may develop into hemiatrophy (Rosenthal[50]). Cords[3] called *sclerodermie en coup de sabre* a "streaklike facial atrophy." Ehrmann and Brünauer[51] compiled the literature on this subject.

It is remarkable that scleroderma *en coup de sabre* is located in the paramedian area, corresponding exactly to the area of loss of hair seen in the first 3 cases of the present series. Stühmer[52] pointed out that in scleroderma *en bandes* the disturbance is apparently located in the median, but is actually in the paramedian, area. Harris[5] said of morphea:

> A noteworthy point is that the trophic loss described as greyness, baldness and atrophy of the bones of the face and the skin does not extend as far inward as the middle line, but ceases about the line of the supraorbital notch.

I should hardly hesitate to ascribe the morphea in his case to abortive progressive facial hemiatrophy with typical localization of loss of hair in the paramedian area. The same applies to the cases of Mitchell,[53] Ehrmann and Brünauer[51] and Spillmann.[54] Flint,[31] in describing a case of facial hemiatrophy, spoke of a *coup de sabre* deformity. In some cases of facial hemiatrophy the *sclerodermie frontale en coup de sabre* constituted an integral part of the whole clinical picture (Bory[12]). Numerous other reports could be mentioned illustrating the localization of what is known as sclerodèrma in the paramedian area in which alopecia, blanching of the hair and atrophy are found in cases of facial hemiatrophy. Therefore, the assumption is justified that what has been known as scleroderma *en coup de sabre* is nothing but an abortive form of progressive facial hemiatrophy, the progression of which stopped very early. The similarity of these two conditions is clearly seen in the reports of Osborne,[9] O'Leary and Nomland[55] and Tauber and Goldman.[10]

### BORDERLINE FORMS OF PROGRESSIVE FACIAL HEMIATROPHY

It is most interesting that besides hemiatrophic and sclerodermatous lesions, other pathologic conditions are located often in the paramedian area, such as nevi (Bailey,[56] Meirowsky[57] [his figures 7, 38, 39]), moles (Roussy and associates[58]), congenital partial whiteness of the eyelashes (Streatfeild[59]) and grayness of the hair (Cheatle[60]). From observations, I, too, gained the definite impression that this paramedian area represents a place of predilection for malformation and other morbid conditions of the skin, of many varieties. All these may be classified as "paramedian facial cutaneous dystrophy." In some of these cases the condition may be regarded as abortive facial hemiatrophy, and in some as congenital malformation of the skin; in some only changes in the skin or hair are seen; in some the disease is slightly progressive; in some the condition remains unchanged, but in all cases the dystrophy is located on a streak parallel to the median line and at some distance from it. Examples of such a paramedian facial cutaneous dystrophy are given here.

CASE 11.—A 42 year old laborer showed discoloration of his facial hair, of which he was hardly aware (fig. 11). On the left side, the inner fourth of his eyebrow and eyelashes was white; the rest was dark. There was much white on the left side of his mustache, especially on the outer part of the lip. There were

48. Ben, F.: Hemiatrophia faciei und Sklerodermie, Dermat. Wchnschr. **83**:1366, 1926.

49. Truffi, G.: Emiatrofia facciale sinistra con sclerodermia circoscritta, Dermosifilografo **8**:90, 1933.

50. Rosenthal, O.: Ueber einen Fall von partieller Sklerodermie, mit Uebergang in halbseitige Gesichtsatrophie, combiniert mit alopecia areata, Berl. klin. Wchnschr. **26**:755, 1889.

51. Ehrmann, S., and Brünauer, St. R.: Sclerodermie, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol. 8, pt. 2, p. 717.

52. Stühmer, in discussion on Vohwinkel: Sclerodermie en bandes et en plaques, Zentralbl. f. Haut- u. Geschlechtskr. **27**:586, 1928.

53. Mitchell, J. H.: Scleroderma Circumscriptum en Coup de Sabre, Arch. Dermat. & Syph. **34**:115 (July) 1936.

54. Spillmann, L.: Sclérodermie lardacée en coup de sabre de la région frontale: Crises épileptiformes concomitantes, Rev. méd. de l'est **30**:597, 1898.

55. O'Leary, P., and Nomland, R.: A Study of One Hundred and Three Cases of Scleroderma, Am. J. M. Sc. **180**:95, 1930.

56. Bailey, P.: Intracranial Tumors, Springfield, Ill., Charles C Thomas, Publisher, 1933, case XX, fig. 81.

57. Meirowsky, E.: Die angeborenen Muttermäler und die Färbung der menschlichen Haut im Lichte der Abstammungslehre, Jena, Gustav Fischer, 1920, figs. 7, 38 and 39.

58. Roussy, G.; Lévy, G., and Rosenrauch, C.: L'origine médullaire de certaines rétractions de l'aponévrose palmaire [fig. 2], Ann. de méd. **31**:21, 1932.

59. Streatfeild, J. F.: Observations on Some Congenital Diseases of the Eye, Lancet **1**:263, 1882.

60. Cheatle, G. L.: The Incidence of the Hair's Greyness, Brit. M. J. **2**:176, 1905.

no other changes in the hair or skin. The spots in which the eyebrow, eyelashes and mustache on the left showed the greatest discoloration were on a vertical line, all at the same distance from the midline.

CASE 12.—A 60 year old man showed very mild white discoloration of the medial portion of his left eyebrow and conspicuous and nearly complete white discoloration of the medial part of the lashes of his

Fig. 11 (case 11).—Left-sided blanching of the eyebrows, eyelashes and mustache in the paramedian area.

Fig. 12 (case 12).—Left-sided blanching of the eyelashes in the paramedian area.

left eye (fig. 12). He could give no definite information as to the beginning or the course of this discoloration.

CASE 13.—A 19 year old youth showed some spots of white in the hair on the left side of his head, in the temple area. Most evident was the discoloration of the hair on the medial edge of his left eyebrow, in the paramedian area.

CASE 14.—A 45 year old man showed a pigmented area on the left side of his forehead close to the midline and running parallel to the midline from the hair line to the eyebrow (fig. 13). There were no other changes. The patient stated that the pigmentation might have developed within the last few years.

CASE 15.—A 42 year old man showed a pigmented area, without any other changes in the skin, on the right side of the forehead, beginning in the midline and extending about 1 fingerbreadth (fig. 14). Details of development are not available, but the condition certainly was not congenital.

Cognizance is taken of these peculiar neurodermatologic changes, although their pathophysiologic significance cannot be appraised exactly. It is especially difficult to say how far one may go in any one case in classifying the condition as

Fig. 13 (case 14).—Nevus flammeus on the left side of the forehead parallel to the midline.

Fig. 14 (case 15).—Nevus flammeus on the right side of the forehead near the midline in the same area in which abortive facial hemiatrophy is seen in figure 7 (case 8).

abortive facial hemiatrophy. But there is little doubt that in every single case there is some relation to this disease and that, by paying attention to changes in the skin in the paramedian area of the face, one might be able to diagnose the disease in its very early stages.

### PARAMEDIAN AREA

The location and extent of this paramedian area are peculiar. They do not correspond to any peripheral branch of the trigeminus nerve or to onion-peel-like areas in cases of lesions of

the nucleus of the trigeminus nerve. There is nothing that would suggest a connection with the embryonic closure lines of the face (Fischer [61]), nor does the paramedian area correspond to the area in which the various branches of the trigeminus nerve become cutaneous. The median line extends more medially than the points of emergence of the trigeminal branches. The first hemiatrophic manifestations often are found on the forehead in an area remote from the point at which the first branch of the fifth nerve becomes cutaneous.

The following hypothesis is a possible interpretation of the peculiar site of this paramedian area: In hemiatrophy the central part of the face is affected either not at all or late in the disease. The part first and most intensively affected is, as has been seen, a vertical streak running parallel to the midline and at some distance lateral to it. The median part of the face obtains its nerve supply from both sides. It is known that the cutaneous nerves of the face transgress the median line from both sides. Therefore, the nerve fibers overlap in the middle line to an extent that varies much individually. A rough comparison would be to imagine that in trophic innervation the two vertical halves of the body are joined together in dovetailed fashion, like two pieces of wood with alternate interlocking. The trophism of the middle part of the face is secured from both sides and does not suffer from a unilateral lesion. But the area of the skin located laterally, in which the double innervation ceases and the unilateral innervation begins, must be, so to speak, a weak spot in the trophic innervation and therefore is susceptible to pathologic changes. It is in this paramedian area that one must look for the beginning of hemiatrophic or other pathologic changes.

### THE BRAIN IN PROGRESSIVE FACIAL HEMIATROPHY

Striking and significant features of the first 3 cases were the signs and symptoms of involvement of the brain. In the literature frequent mention is made of cerebral manifestations in cases of hemiatrophy. Beer,[62] in 1898, found cerebral symptoms in 15.54 per cent of 148 collected cases. Two kinds of cerebral involvement are recognized. The first is a more or less diffuse involvement of the brain; the second, more significantly, is an involvement of the brain on the side of the hemiatrophy. In the first category belong the cases of Bannister,[63] Bergson,[64] Delamare,[65] Mendel [66] and Romberg,[82] who reported the association of hemiatrophy with mental disease. Arteriosclerosis of the cerebral vessels or encephalomalacia was found by Jolly,[67] Orbison,[68] Parry,[69] Pissling [70] and Touche.[71] Encephalitic processes were assumed by Friedreich,[72] Henschen,[73] Hrach,[74] Meyer,[75] Raymond and Sicard [76] and Tedeschi.[77] A diagnosis of pain of central origin was made by Stief [78] and Wolff.[79] Numerous authors found hemiatrophy associated with migraine (Boenheim,[80] Bruns,[81] Cornu,[82] Herz,[83] Holtzapple,[84] Mollaret,[85] Reiss,[86] Salus,[87]

61. Fischer, O.: Ein Beitrag zur Lehre von der Hemiatrophia facialis progressiva, Monatschr. f. Psychiat. u. Neurol. **14**:366, 1903.

62. Beer, M.: Beitrag zur Kenntnis der Hemiatrophia facialis progressiva, Inaug. Dissert., Königsberg i. Pr., L. Krause & Ewerlein, 1898.

63. Bannister, H. M.: Progressive Facial Hemiatrophy, J. Nerv. & Ment. Dis. **3**:539, 1876.

64. Bergson: De Prosopodysmorphia, Inaug. Dissert., Berlin, Nietack, 1837.

65. Delamare: Contribution à l'histoire de l'aplasie lamineuse progressive de la face, Rec. de mém. de méd. mil. **36**:484, 1880.

66. Mendel, E.: Ein Fall von halbseitiger Gesichtsatrophie, Neurol. Centralbl. **1**:268, 1883.

67. Jolly: Ueber multiple Hirnsklerose, Arch. f. Psychiat. **3**:711, 1877.

68. Orbison, T.: Trophic Hemiatrophia: Complete, J. Nerv. & Ment. Dis. **35**:695, 1908.

69. Parry, C. H.: Collections from unpublished papers, London, Underwood, 1825, vol. 1, p. 478.

70. Pissling: Mitteilungen aus der Praxis, Ztschr. d. k.-k. Gesellsch. d. Ärzte zu Wien **1**:496, 1852.

71. Touche: Deux cas d'hémiatrophie faciale, Rev. neurol. **10**:375, 1902.

72. Friedreich: Progressive Muskelatrophie, Berlin, A. Hirschwald, 1873.

73. Henschen, S. E.: Hemiatrophia progressiva, Nord. med. Ark. **15**:1, 1883; abstracted, Neurol. Centralbl. **1**:374, 1883.

74. Hrach: Ueber einen Fall von angeborener neurotischer Hemiatrophie, Wien. med. Wchnschr. **54**: 343, 1904.

75. Meyer, E.: Totale Hemiatrophie, Neurol. Centralbl. **29**:450, 1910.

76. Raymond and Sicard: Trophonévrose hémiatrophique totale et familiale, Rev. neurol. **13**:593, 1902.

77. Tedeschi: Paralysie spinale infantile aiguë avec hémiatrophie de la face, Rev. neurol. **13**:42, 1905.

78. Stief, A.: Ueber einen Fall von Hemiatrophie des Gesichtes mit Sektionsbefund, Ztschr. f. d. ges. Neurol. u. Psychiat. **147**:573, 1933.

79. Wolff, H. G.: Progressive Facial Hemiatrophy, Arch. Otolaryng. **7**:580 (June) 1928.

80. Boenheim: Zur Pathogenese der Hemiatrophia faciei progressiva, Deutsche Ztschr. f. Nervenh. **65**: 219, 1920.

81. Bruns: Hemiatrophia facialis progressiva, Neurol. Centralbl. **16**:511 1897.

82. Cornu, E.: Contribution à l'étude des migraines et de leurs rapports avec les états épileptiques et délirants, Thesis, Lyon, no. 144, 1902.

83. Herz, M.: Ueber Hemiatrophia facialis progressiva, nebst Mittheilung eines diesbezüglichen Falles, Arch. f. Kinderh. **8**:241, 1886-1887.

84. Holtzapple, cited by Flatau, E., in Lewandowsky, M.: Handbuch der Neurologie, Berlin, Julius Springer, 1914, vol. 5, p. 400.

*(Footnotes continued on next page)*

Souques and Bourguignon,[88] Oppenheim [29] and Wolff [89]). Of special interest are those cases in which the migraine was localized homolaterally. Wolff reported the case of a 23 year old woman with hemiatrophy of the right side of the face who had been suffering from right-sided migraine headaches since the age of 12 years. The unilateral head pain in Diller's [13] case was "always strictly confined to the right side," the side of the hemiatrophy. Klingmann's [6] patient had hemiatrophy of the right side of the face and complained of constant pain in the right occipital region. The patient in case 1, with hemiatrophy of the right side of the face, had knifelike pains through the right side of her head.

In numerous cases the hemiatrophy was associated with epilepsy. The following authors may be mentioned: Archambault and Fromm,[1] Bost,[90] Bragman,[91] Brunner,[92] Buzzard,[92] Černi,[93] Chasanow,[46] Diller,[13] Donley,[94] Emminghaus,[95] Hallager,[92] Kiely,[96] Kopczynski,[97] Lande,[98] Lauber,[16] MacBride,[99] Merritt, Faber and Bruch,[100] Merzejewsky,[92] M. Meyer,[101] O. B. Meyer,[102] Neustaedter,[103] Osborne,[9] Schultze,[104] Stiefler,[22] Thiel,[105] Vivado,[24] Wolfe and Weber [28] and Zeller.[106] Except in a few cases, as, for instance, in that of Bragman [91] and in my case 3, the epilepsy was a late manifestation. In the light of the foregoing discussion regarding the relationship of scleroderma *en coup de sabre* and hemiatrophy, it is remarkable that Spillmann [54] and Josefowitsch [107] reported the association of epilepsy and scleroderma.

Tauber and Goldman [10] and Pollock [108] expressed the belief that of all complications of hemiatrophy, epilepsy is the most frequent. This statement could hardly be maintained, even in the light of the numerous cases cited. On the other hand, one can hardly subscribe to the opinion of Archambault and Fromm,[1] who stated:

> There is nothing astonishing in the fact that, rare as it is, facial hemiatrophy should occasionally appear in a person suffering from so common a disease as epilepsy.

That the combination of epilepsy and hemiatrophy cannot be regarded as purely accidental is proved by the cases in which the epileptic phenomena, mostly of the sensory jacksonian type, were confined to the heterolateral half of the body, as in my cases 1 and 2. I may cite Barkman,[109] Sainton and Baufle,[110] Walsh [37] (his case 2), Donley [94] and Diller.[13] In some cases signs of involvement of the pyramidal tract have been found on the contralateral side of the body (Bernstein,[11] Jumentié and Krebs [111] and MacBride [99]). Such signs, though mild, could be demonstrated on the contralateral side in cases 1, 2 and 3 of the present series. Merritt, Faber and Bruch [100] and Thiel [105] found cerebral calcification. The involvement of the homolateral hemisphere in cases of hemiatrophy, as shown

85. Mollaret, P.: Contribution à l'étude clinique et histologique de l'hémiatrophie faciale progressive, Rev. neurol. **2**:463, 1932.

86. Reiss: Hemiatrophia facialis progressiva, München. med. Wchnschr. **63**:1331, 1916.

87. Salus, F.: Beginnende Hemiatrophia facialis progressiva, Zentralbl. f. Haut- u. Geschlechtskr. **33**: 777, 1930.

88. Souques and Bourguignon: Un cas d'hémiatrophie progressive de la face amélioré par l'ionisation calcique, Rev. neurol. **29**: 204, 1922.

89. Wolff, H. G.: Progressive Facial Hemiatrophy, J. Nerv. & Ment. Dis. **69**:140, 1929.

90. Bost, C.: Progressive Facial Hemiatrophy, Arch. Pediat. **44**:497, 1927.

91. Bragman, L. J.: Progressive Facial Hemiatrophy: An Early Case, Arch. Pediat. **52**: 686, 1935.

92. Cited by Marburg.[42]

93. Černi, L.: Two Cases of Hemiatrophia unilateralis totalis, Sovrem. psikhonevrol., vol. 3, p. 494, 1926.

94. Donley, D. E.: Facial Atrophy Associated with Epilepsy, J. Nerv. & Ment. Dis. **82**:33, 1935.

95. Emminghaus, H.: Ueber halbseitige Gesichtsatrophie, Deutsches Arch. f. klin. Med. **11**:96, 1873.

96. Kiely, C. E.: A Case of Facial Hemiatrophy with Convulsions, J. Nerv. & Ment. Dis. **58**:229, 1923.

97. Kopczynski: Hemiatrophia faciei progressiva, Neurol. Centralbl. **28**:778, 1909.

98. Lande, L.: Essai sur l'aplasie lamineuse progressive, Thesis, Paris, no. 278, 1869.

99. MacBride, H. J.: Case of Facial Hemiatrophy, Brain **48**:133, 1925.

100. Merritt, K. K.; Faber, H. K., and Bruch, H.: Progressive Facial Hemiatrophy, J. Pediat. **10**:374, 1937.

101. Meyer, M.: Ein Fall von fortschreitender linksseitiger Gesichtsabmagerung, Berl. klin. Wchnschr. **7**:23, 1870.

102. Meyer, O. B.: Lipodystrophia progressiva, München. med. Wchnschr. **66**:253, 1919.

103. Neustaedter, M.: A Case of Facial Hemiatrophy, M. Rec. **85**: 700, 1914.

104. Schultze: Hemiatrophia faciei, Deutsche med. Wchnschr. **40**:1290, 1914.

105. Thiel, R.: Roentgendiagnostik des Schädels bei Erkrankungen des Auges, Berlin, Julius Springer, 1932, case 2, figs. 44-47.

106. Zeller: Fall von rechtsseitiger Hemiatrophia facialis, Neurol. Centralbl. **2**:119, 1883.

107. Josefowitsch, cited by Ehrmann and Brünauer.[51]

108. Pollock, L. J.: Progressive Facial Hemiatrophy, Arch. Neurol. & Psychiat. **33**:888 (April) 1935.

109. Barkman, A.: Ein Fall von Hemiatrophia faciei progressiva mit epileptischen Anfällen, Deutsche Ztschr. f. Nervenh. **75**:1, 1922.

110. Sainton, P., and Baufle: L'hémiatrophie faciale, Gaz. de hôp. **83**:1841, 1910.

111. Jumentié, J., and Krebs, E.: Un cas d'hémiatrophie faciale progressive gauche avec hémiparésie et crises d'épilepsie bravais-jacksonienne du côté droit. Rev. neurol. **26**:117, 1913.

by Brain,[112] is of great significance. He reported a case "in which left facial hemiatrophy was associated with right-sided epilepsy, hemiplegia, hemianaesthesia, hemianopia and aphasia." The encephalogram showed marked dilatation of the ventricle on the left side and atrophy of the left hemisphere. The involvement of the homolateral hemisphere of the brain in cases of hemiatrophy, proved by clinical, pathologic and roentgenographic examinations, excludes mere coincidence. Generally speaking, the intimate ontogenetic relations between skin and brain make their simultaneous involvement understandable. Reference may be made to the vast and diversified group of congenital neuroectodermal dysplasias, especially to the common association of facial and intracranial hemangiomas.

### CARDINAL SYMPTOM OF PROGRESSIVE FACIAL HEMIATROPHY

Cerebral involvement usually constitutes the last link in the chain of the extremely diversified symptoms of facial hemiatrophy. The disease presents such an immense variety of pathologic phenomena that they could hardly all be the direct result of a single lesion, wherever it may be and however intensive or extensive. The pathologic phenomena observed in some cases may be of indirect or secondary nature, and not invariably immediately or directly connected with the primary lesion.

Thus, especially with regard to the late cerebral manifestations, the questions arise: What are the primary, essential symptoms of hemiatrophy? What is on the "must list" of its symptoms? It is the fat and subcutaneous tissues which are primarily, and sometimes exclusively, affected. There is no case of hemiatrophy in which they are not involved. In some cases, of course, many other structures are also affected. But the starting point, at which the disease may stop, is the atrophy of fat and subcutaneous tissues. For instance, in the cases of Pichler,[113] Recht[114] and Strasburger,[115] in which the disease certainly was facial hemiatrophy, only unilateral atrophy of the fat of the cheek was present. In many a case the atrophy of the fat and subcutaneous tissues is so predominant as to be nearly exclusive (Calmette and Pagès[116]). Many authors have emphasized that the skin was completely intact (Cox and Maclure,[36] Donley,[94] Grünmandel,[117] Hoeflmayer,[118] Hoffmann,[119] Jendrassik,[14] Krüger,[120] Lauerbach,[43] Léri,[17] Luxenburger,[121] La Maire,[122] Stief[78] and Werba[123]) or little affected (Levkovski[124] and Smirnitski[125]). In some of my own cases the skin was only mildly affected or not at all. Even histologically, the skin in case 2 was normal. Changes in the skin may or may not follow atrophy of the fat and subcutaneous tissues. If they follow it, they may occur late in the disease. The predominant or exclusive involvement of the subcutaneous tissues induced Bitot and his pupil Lande,[98] in 1869, to call the disease *aplasie lamineuse progressive,* or *atrophie du tissu connectif,* and to regard it as *une affection propre, spéciale antopathique et protopathique de l'élément lamineux.* Neither the trigeminus nerve nor the cervical sympathetic chain is necessarily involved in cases of hemiatrophy. Many authors have stressed explicitly that no symptoms referable to the trigeminal nerve or the sympathetic nervous system could be observed (Cox and Maclure,[36] Hoeflmayer,[118] Kopczynski,[97] Salomon,[126] Stier[127] and Vazquez Rodriguez[128]). Lange (cited by Smirnitski[125]) found in a series of 163 cases only 18 in which there were sympathetic disturbances. In most of my own cases

112. Brain, R.: Diseases of the Nervous System, ed. 2, London, Oxford University Press, 1940, p. 599.

113. Pichler, K.: Einseitiger Schwund des Wangenfett-Propfes, Deutsche Ztschr. f. Nervenh. **61**:181, 1918.

114. Recht, G.: Zur Kasuistik des halbseitigen Wangenfettschwundes, Deutsche Ztschr. f. Nervenh. **134**:237, 1934.

115. Strasburger, J.: Ueber umschriebenen Fettgewebschwund des Gesichts, Med. Klin. **26**: 981, 1908.

116. Calmette and Pagès: Un cas d'hémiatrophie faciale progressive, Nouv. iconog. de la Salpêtrière **16**:26, 1903.

117. Grünmandel, S.: Hemiatrophia facialis incompleta, Zentralbl. f. Haut- u. Geschlechtskr. **18**:753, 1926.

118. Hoeflmayer, L.: Ein Fall von halbseitigem Gesichtsschwund, München. med. Wchnschr. **45**:391, 1898.

119. Hoffmann, A.: Zur Kenntnis der Hemiatrophia faciei progressiva, Neurol. Centralbl. **19**:999, 1900.

120. Krüger, H.: Ein Fall von Hemiatrophia faciei progressiva mit Sensibilitätsstörungen und gleichseitigen tonisch-klonischen Kaumuskelkrämpfen, Neurol. Centralbl. **35**:17, 1916.

121. Luxenburger, A.: Ueber zwei Fälle von Hemiatrophia facialis progressiva, München. med. Wchnschr. **48**:1413, 1901.

122. Le Maire, M.: A Case of Facial Atrophy, abstracted, Neurol. Centralbl. **17**:509, 1898.

123. Werba, D. H.: Hemiatrophy of the Face, M. Bull. Vet. Admin. **17**:291, 1941.

124. Levkovski, A. M.: Unilateral Progressive Atrophy of the Face, Obozr. psikhiat., nevrol. **7**:401, 1902.

125. Smirnitski, I. N.: Pathogenesis of Hemiatrophia Faciei, Zhur. nevropat. i psikhiat. **22**:599, 1929.

126. Salomon, S.: Ein Fall von Hemiatrophia progressiva mit Augennervensymptomen, Neurol. Centralbl. **26**:614 and 846, 1907.

127. Stier, E.: Ueber Hemiatrophie und Hemihypertrophie nebst einigen Bemerkungen über ihre laterale Lokalisation, Deutsche Ztschr. f. Nervenh **44**: 21, 1912.

128. Vazquez Rodriguez, A.: Un caso di hemitrofia facial, Pediatria españ. **16**:135, 1927.

there was no involvement of the trigeminus nerve or of the sympathetic system—except, of course, the trophic function of the latter. Therefore, the atrophy of the fat and subcutaneous tissues must be regarded as the primary and leading symptom of facial hemiatrophy.

### EXTRAFACIAL EXTENSION OF THE ATROPHY

The involvement of the fat and subcutaneous tissues is by no means restricted to the face, as might be implied from the term "facialis." Since the atrophy primarily affects the frontal part of the head, the term "hemiatrophia frontalis progressiva" would be more appropriate. In many instances the atrophy has transgressed the boundary of the face. Saenger [129] stressed the involvement of the area of the nervus auricularis magnus and the nervus occipitalis minor. Oppenheim [29] and Fischer [61] found the upper triangle of the neck to be the starting point of the atrophic process. Archambault and Fromm [1] found that the process had initially developed in the domain of the second and third cervical roots. Stief [78] reported the extension of the atrophy to the shoulder. Several authors observed involvement of the homolateral arm (Bouveyron,[130] Collins,[131] Debray [131] and Vassilevski [23]). Remarkable are the cases of abortive involvement of the trunk homolaterally. Thus, Leskowski [33] found an atrophic strip similar to that of the face in the intercostal space between the eighth and the ninth rib. Extrafacial atrophic spots on the trunk were observed by Brunner,[92] Jendrassik [14] and Soltmann.[92] Several authors (Bernstein,[11] Heinemann [132] and Martin [133]) observed atrophy of the breast homolaterally. Raymond and Sicard [76] distinguished a definite type of hemiatrophy, "typus hemi-facio-scapulo-humero-thoracicus," several forms of which were found by Sternberg,[134] Virchow [135] and Wahl and Christian.[136] In a postmortem examination, Harbitz [137] observed that the kidney on the affected side was hypoplastic. Stief [78] found atrophy of the internal organs homolaterally, including the vocal cord, kidney, adrenal gland and ovary. Finally, cases in which complete hemiatrophy affected one half of the entire body have been observed. In addition to the cases mentioned by Archambault and Fromm,[1] the cases of the following authors may be cited: Collins,[131] Černi,[93] Chasanow,[46] Finesilver and Rosow,[138] Henschen,[73] Kroll,[47] Masten,[139] Nemlicher and Rappoport,[140] Orbison [68] and Vivado.[24] The case of Pelizaeus,[141] in which the hemiatrophy began in the left arm and extended to the left leg but spared the face and thorax, is unique. The atrophic process may even begin in the leg. According to Wilson,[142] a patient of Campbell's had atrophy of the fat of the entire right foot, and even the bones seemed to have suffered some atrophy. Campbell attributed the condition to facial hemiatrophy. Savill (cited by Wilson [142]) established an even closer relationship in a case in which a similar condition was associated with definite facial hemiatrophy. The involvement of other parts of the body, that is, on the same side as the facial atrophy, often may be not only abortive and minimal but latent, and therefore is frequently overlooked. In the case of Stief,[78] in which only the shoulder was involved, marked diminution of the sweat secretion was found homolaterally with Minor's test. Examples of every possible extension of hemiatrophy are reported in the literature, ranging from the initial form, in which only the forehead is affected, to complete involvement of one half of the body.

### IRRITATIVE PHENOMENA ASSOCIATED WITH PROGRESSIVE FACIAL HEMIATROPHY

The physiopathologic process that leads to hemiatrophy must be an active one, a surplus of innervation which brings about destruction of

129. Saenger: Hemiatrophia faciei, Neurol. Centralbl. **31**:607, 1912.

130. Bouveyron: De l'hémiatrophie faciale dans ses rapports avec les lésions du ganglion cervical inférieur, Rev. neurol. **10**:211, 1902.

131. Cited by Cassirer and Hirschfeld, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1935, vol. 17, p. 246.

132. Heinemann, W.: Ueber Hemiatrophia faciei, Inaug. Dissert, Leipzig, B. Georgi, 1907.

133. Martin, J. P.: A Case of Facial Hemiatrophy with Lack of Development of the Breast on the Same Side, Brain **48**:140, 1925.

134. Sternberg: Ueber eine besondere Form der Hemiatrophia faciei, Arch. f. Psychiat. **99**:815, 1933.

135. Virchow: Ueber neurotische Atrophie, Berl. klin. Wchnschr. **17**:409, 1880.

136. Wahl, W., and Christian, P.: Ueber einen Fall von idiopathischer Hemiatrophia humero-scapulothoracalis mit anämischen und telangiektatischen Naevi und Irisheterochromie, Deutsche Ztschr. f. Nervenh. **144**:1, 1937.

137. Harbitz: Akromegalie und Hemiatrophia facialis progressiva, Zentralbl. f. allg. Path. u. path. Anat. **22**:801, 1911.

138. Finesilver, B., and Rosow, H. M.: Total Hemiatrophy, J. A. M. A. **110**:366 (Jan. 29) 1938.

139. Masten, M. G.: Asymmetry: Unilateral Atrophy and Facial Hypertrophy, Arch. Neurol. & Psychiat. **35**:136 (Jan.) 1936.

140. Nemlicher, L. J., and Rappoport, B. J.: Hemiatrophy of Face and Body Combined wth Idiopathic Dermatologic Processes, Vrach. delo **8**:278, 1925.

141. Pelizaeus: Ueber einen ungewöhnlichen Fall von progressiver Hemiatrophie, Neurol. Centralbl. **16**: 530, 1897.

142. Wilson, S. A. K.: Neurology, edited by A. Ninian Bruce, Baltimore, William Wood & Company, 1940, vol. 2, p. 1049.

tissues. It is not merely hypotrophy or underdevelopment but an actual disintegration of tissue. Progressive facial hemiatrophy can be distinguished easily from facial asymmetry, congenital hypotrophy or hypotrophy due to disease, such as cerebral palsy in children, facial paralysis, poliomyelitis pontis or torticollis. In these conditions there is simply a retardation in growth, a minus of activity, whereas in hemiatrophy a plus of activity and an increase of reflexive activity seem to be prevalent.

Since the trophism of the fat and subcutaneous tissues is unquestionably under the influence of the sympathetic nervous system, facial hemiatrophy is a disorder in which the centers and tracts of the sympathetic system that are concerned with the metabolism of fat and of the subcutaneous tissues are essentially and primarily involved. Many authors have assumed that a pathologic state of irritation leads to facial hemiatrophy (Chasanow,[46] Goering[143] Müller,[144] Cassirer,[45] Stilling,[145] Kroll[47] and Brüning[146]). It is for this reason that periarterial sympathectomy was recommended for facial hemiatrophy. This operation was performed with some success, as reported by Brüning,[146] Forster,[131] Leriche[131] and Trepte.[147] From their pharmacodynamic tests, Marinesco, Kreindler and Façon[148] concluded that hemiatrophy was due to hyperfunction of the sympathetic nervous system. By using the epinephrine test of Muck and the sweating test of Minor, Joël[149] found in 4 cases irritative phenomena in the peripheral sympathetic system of the area involved. This does not exclude the possibility that, with this hyperfunction of the vegetative system, its hypofunction may coexist or develop later (Smirnitski[125]). Oppenheim[29] observed cases in which symptoms of paralysis and irritation of the sympathetic nervous system were present.

While the cardinal symptom of hemiatrophy, the atrophy of fat and subcutaneous tissues, indicates a state of irritation in the trophic sympathetic system, this state of irritation and hypertonus definitely extends over other functions of the sympathetic nervous system and may spread to the cranial and the spinal nerves. In the area affected by the hemiatrophy, phenomena of irritation predominate and often precede those of palsy. The following symptoms of sympathetic involvement may be present: mydriasis, exophthalmos, hyperhidrosis, heterochromia of the iris (as in my case 1), conjunctival injection (Hughes,[150] and Werba[123])—with similar findings in case 5 of this series—rhinorrhea, nevi, pigmentation, vitiligo, alopecia, blanching of the hair, scleroderma, *mal perforant* and Raynaud's disease. The secretion of sweat and sebum is often increased at first and decreased later. On microscopic examination of the capillaries, Pollak[151] found signs of a "spastic-atonic vasoneurosis." Signs indicating a state of irritation in the cranial nerves have often been observed. They include spasm of the muscles innervated by the facial and trigeminal nerves (Courtet,[152] Hoeflmayer,[118] Jendrassik,[14] Krüger,[120] Nemlicher and Rappoport,[140] Sachs,[153] Vivado[24] and Wirschutzki[154]). Neuralgia in the trigeminal area is common; it begins early; in fact, it is often a precursor of the disease. In the area of the fifth nerve such manifestations as hyperesthesia, tender Valleix pressure points, paresthesia and homolateral hyperesthesia for taste are sometimes observed.

A local disturbance in the metabolism of fat has been considered here as a primary and cardinal feature of hemiatrophy. The peripheral apparatus in charge of the trophism of fat and subcutaneous tissues is evidently in such a state of increased, uncontrolled, unregulated activity that it leads to increased disintegration of tissues and subsequently to atrophy. The trophic influences for the face are not transmitted through the facial nerve but are mediated by the sensory fibers of the trigeminus nerve. However, these fibers do not belong primarily to the trigeminus but are derived from the cervical sympathetic trunk. Thus, the trophic stimulus passes from the sympathetic fibers to the trigeminal nerve in order to reach the tissues. It is easy to under-

143. Goering, D.: Ueber den Einfluss des Nervensystems auf das Fettgewebe, Ztschr. f. Konstitutionslehre **8**:312, 1922.

144. Müller, L. R.: Lebensnerven und Lebenstriebe, Berlin, Julius Springer, 1931; Ueber den Einfluss des Nervensystems auf das Fettgewebe, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **33**:428, 1921.

145. Stilling: Untersuchungen über die Spinal-Irritation, Leipzig, O. Wigand, 1840, p. 325.

146. Brüning, F.: Die tropische Funktion der sympathischen Nerven, Klin. Wchnschr. **2**:67, 1923.

147. Trepte, G.: Hemiatrophia totalis mit Sclerodermie und Sympathicusoperation, Ztschr. f. d. ges. Neurol. u. Psychiat. **124**:809, 1930.

148. Marinesco, Kreindler and Façon: Sur la pathologie de l'hémiatrophie faciale, Paris méd. **13**:269, 1932.

149. Joël, W.: Ueber Hemiatrophia faciei progressiva, Inaug. Dissert., Berlin, 1932.

150. Hughes, W. N.: Progressive Facial Hemiatrophy, J. Nerv. & Ment. Dis. **84**:683, 1936.

151. Pollak, F.: Ein eigenartiger Fall von einseitiger Hemiatrophie und seine Beziehungen zum vegetativen Nervensystem, Arch. f. Dermat. u. Syph. **159**:188, 1930.

152. Courtet: Atrophie unilatérale de la face, Gaz. hebd. de méd. **13**:196, 1876.

153. Sachs, B.: Progressive Facial Hemiatrophy with Some Unusual Symptoms, M. Rec. **37**:292, 1890.

154. Wirschutzki: Zur Kasuistik der Hemiatrophia facialis progressiva, abstracted, Neurol. Centralbl. **25**: 1008, 1906.

stand that a state of irritation in one of the manifold conductive systems of the trigeminal nerve may be easily transmitted to the other systems which pass through the same nerve. The irritation jumps over to a neighboring tract and sets up irritative phenomena. Other examples of transmission of irritation from one system to another when the systems are conveyed over the same nerve may be cited. Cassirer [45] stated that the most common cause of trophic disturbances is irritation which comes from the sensory tract and is transmitted to the sympathetic nervous system. Unilateral trophic changes occur in the face in cases of long-standing trigeminal neuralgia (Surat [155]). Facial spasm is seen in association with trigeminal neuralgia. Thus it is conceivable that in cases of hemiatrophy irritation in the trophic centers and tracts is transmitted to other tracts of the sympathetic nervous system and to the sensory and motor tracts. A similar mechanism underlies the phenomena of Head's zones. The trophic tracts of the face pass through the cervical sympathetic system and the trigeminus; thus, a concomitant irritation of other vegetative, sensory or motor tracts of the face is possible.

### INFLAMMATORY PROCESSES IN THE AREA OF ATROPHY

Not only irritative phenomena but inflammatory processes occur in the tissues of the atrophic area. These processes may differ widely in location and character. They include neuritis of the facial nerve (Gowers [156]) or of the trigeminal nerve (Mendel,[66] Loebl and Wiesel [157]), herpes (Hoeflmayer [118] and Trotter [158]) and inflammation of the cervical sympathetic ganglia (Brüning [146] and Kroll [47]). Especially common are inflammatory processes involving the eye on the affected side: keratitis neuroparalytica, ulcers, iritis, iridocyclitis, choroiditis, cataract and edema of the papilla (Beer,[62] Chaillous and Thibierge,[159] Emminghaus,[95] Flint,[31] Graff,[160] Mollaret,[85] Morelli,[161] Neustaedter,[103] Stief,[78] Weekers [162] and Wolfe and Weber.[28]). Lauber [16] found tuberculosis of the eye on the affected side. In case 2 of the present series the homolateral eye showed tuberculous infection very early. Involvement of the lymph glands of the neck was observed by Loewy-Hattendorf,[18] Oppenheim [29] and Siebert.[163] Numerous observations of homolateral implication of the lungs and pleura were made. Archambault and Fromm [1] noted the presence of pulmonary tuberculosis in a strikingly large percentage of cases. The following reports may be cited: Barrel,[164] Bouveyron,[130] Černi,[93] Loewy-Hattendorf,[18] Souques,[165] Steven [166] and Weinberg and Hirsch.[167] In a case of hemiatrophy of the face, trunk and extremities, the last-mentioned authors found ulcerations of the affected arm and leg.

Numerous investigations have been made concerning the influence of the sympathetic nervous system on the permeability of the vessels and on inflammation. Cannon [168] showed that "smooth muscle, whether normally stimulated by parasympathetic influences or stimulated or inhibited by sympathetic influences, is rendered more excitable to chemical agents by destruction of the ultimate innervating neurones." Recent experiments of Asher [169] demonstrated this influence of the sympathetic system:

> If on one side the cervical sympathetic is cut and both eyes are exposed to the rays of a quartz lamp of the same intensity and duration, either only the cornea of the side without sympathetic shows lesions, or, if both corneas have been affected, on the side without sympathetic the lesions are more severe and take longer to heal.[169a]

Orr and Sturrock [170] studied experimentally the

155. Surat, W. S.: Ueber einseitige Störung der Gesichtstrophik, Monatschr. f. Psychiat. u. Neurol. **77**: 202, 1930.

156. Gowers, W. R.: The Influence of Facial Hemiatrophy on the Facial and Other Nerves, Rev. Neurol. & Psychiat. **4**:1, 1906.

157. Loebl, H., and Wiesel, J.: Zur Klinik und Anatomie der Hemiatrophia facialis progressiva, Deutsche Ztschr. f. Nervenh. **27**:355, 1904.

158. Trotter, W.: Recurrent Herpes Zoster of the Face with Hemiatrophy, Proc. Roy. Soc. Med. (Sect. Dermat.) **4**:43, 1915-1916.

159. Chaillous and Thibierge: Iritis chez une malade atteinte d'hémiatrophie de la face, Arch. d'opht. **43**:55, 1926.

160. Graff, H.: Ein Fall von Hemiatrophia facialis progressiva verbunden mit neuroparalytischer Ophthalmie, Inaug. Dissert., Dorpat, H. Laakmann, 1886.

161. Morelli: Dystrofie et trofoneurose, Gazz. d. osp. **2**:1528, 1905.

162. Weekers: Hemiatrophie faciale, Rev. neurol. **28**:1154, 1921.

163. Siebert, H.: Ein Fall von rechtsseitiger Gesichtsmissbildung mit Erscheinungen der Hemiatrophia faciei, Deutsche Ztschr. f. Nervenh. **56**:320, 1917.

164. Barrel, E.: De l'hémiatrophie faciale, Thesis, Lyon, no. 132, 1902.

165. Souques: Syndrome oculo-papillaire, Bull. et mém. Soc. méd. d. hôp. de Paris **19**:484, 1902.

166. Steven, J. L.: Case of Scleroderma, Glasgow M. J. **50**:401, 1896.

167. Weinberg, F., and Hirsch, F.: Hemiatrophia facialis progressiva bei chronischen Lungenaffektionen, etc., Deutsche Ztschr. f. Nervenh. **66**:205, 1920.

168. Cannon, W. B.: A Law of Denervation, Am. J. M. Sc. **198**:737, 1939.

169. Asher, L.: (*a*) Report on the Mode of Action of the Sympathetic and Its Integrative Function, abstracted, International Neurological Congress, London, 1935, p. 37; (*b*) Trophic Function of the Sympathetic Nervous System, J. A. M. A. **108**:720 (Feb. 27) 1937.

170. Orr, D., and Sturrock, A. C.: Toxi-Infective Lesions in the Central Nervous System, Lancet **2**:267, 1922.

lesions found when after division of the cervical sympathetic trunk general intoxication had been produced. Their conclusion was that "the sympathetic nervous system is an important factor in the localization of lesions, not only in the central nervous system but probably wherever they may occur." The influence of the sympathetic nervous system on the pial vessels has been shown conclusively in the experiments of Forbes and Wolff,[171] who used the method of direct inspection through a skull "window." A definite contraction of the pial arteries could be seen on excitation of the cervical sympathetic trunk. On stimulation of the cervical sympathetic chain in unanesthetized cats, Thomas [172] found slight constriction of the ipsilateral pial arterioles. The histopathologic changes found by Stief [78] in a case of facial hemiatrophy showed conclusively the influence of the cervical sympathetic fibers on the vasomotor regulation of the cerebral vessels.

Every tissue deprived of its normal sympathetic innervation provides an area of predilection for infection. Since the vessels of the pia are under sympathetic control, any disturbance of this control renders the corresponding area of the brain more susceptible to toxi-infections. If any toxic or infective process is present in the body, coexistent with facial hemiatrophy, the entire area affected by the hemiatrophy (usually the area of the cervical sympathetic chain, which unilaterally supplies the brain, the head and the area of the upper thoracic segments) is the site of predilection for localization of this process. The infection spreads abundantly in the soil prepared by the derangement of the sympathetic innervation. The affected area yields easily, since it is a locus minoris resistentiae. The inflammatory processes which accompany hemiatrophy and are located in the entire affected area can be thus easily explained. This area includes the brain, which in its homolateral half shows a predilection for encephalitic processes. In case 2, such an encephalitic process was demonstrated histologically. The various pathologic conditions which affect the homolateral half of the brain in cases of facial hemiatrophy can be explained on the basis of disturbed innervation.

*Conclusion.*—It is not the inflammatory or other processes in the area of the cervical sympathetic chain which produce hemiatrophy; it is the reverse; the hemiatrophy is the primary process, which, by weakening the resistance of the affected tissues, makes them the playground for toxi-infections of any kind from anywhere.

171. Forbes, H. S., and Wolff, H. G.: Cerebral Circulation: III. The Vasomotor Control of Cerebral Vessels, Arch. Neurol. & Psychiat. **19**:1057 (June) 1928.

172. Thomas, C. B.: Constriction of Pial Vessels Produced by Stimulation of the Cervical Sympathetic Chain, Am. J. Physiol. **114**:278, 1936.

### CENTRAL ORIGIN OF PROGRESSIVE FACIAL HEMIATROPHY

In order to explain the pathogenesis of hemiatrophy, the existence of a pathologic process has been assumed in the corresponding portion of the sympathetic nervous system which leads to its increased and uncontrolled activity. When this irritation is transmitted to neighboring tracts and centers, it may eventually lead to their paralysis. Since the face is most commonly the seat of the atrophy, the cervical sympathetic trunk must be involved. The question arises whether or not this structure is primarily involved. The fact that inflammatory or traumatic lesions of the cervical sympathetic chain are unable to produce facial hemiatrophy speaks against primary involvement. The case of Seeligmüller [173] which supposedly demonstrated the development of hemiatrophy after injury of the cervical sympathetic trunk, was certainly "not a case of facial hemiatrophy" (Möbius [41]). According to statistics gathered by Kaelin,[174] the cervical sympathetic system was injured in 12 of 1,196 thyroidectomies, but in none of the cases did facial hemiatrophy develop. Naffziger [175] has never seen hemiatrophy after injury to the cervical sympathetic system. It would be difficult to believe that any inflammatory process of the sympathetic nervous system could produce facial hemiatrophy, with its extremely chronic course and its tendency to remain stationary for years, or even decades. The numerous cases of hemiatrophy with only trophic lesions could not be explained on this basis. It had to be assumed that for many years the inflammatory process selects only the trophic mechanism inside the cervical sympathetic chain and spares all others. Patients with hemiatrophy usually show no signs of an inflammatory process in the cervical sympathetic chain. When the extremely insidious beginning and the slow development of the disease are considered, an inflammatory origin appears still more improbable. It may be men-

173. Seeligmüller, A.: Ein Fall von akuter traumatischer Reizung des Halssympathicus, Arch. f. Psychiat. **5**:835, 1875.

174. Kaelin, W.: Ueber Störungen von Seiten des Halssympaticus bei einfacher Struma und im Anschluss an deren operative Behandlung, Leipzig, F. C. W. Vogel, 1915.

175. Naffziger: Personal communication to the author.

ioned that in cases of Trepte [147] and Grabs [176] istologic examination of the cervical sympathetic fibers extirpated surgically showed normal issue. With use of the epinephrine test of Muck nd the sweating test of Minor, Joël [149] was unble to demonstrate in 4 cases any peripheral ausation of the existing irritative phenomena in he sympathetic nervous system.

The increased tonus and the state of irritation n the sympatheic trophic centers and tracts in he area of the hemiatrophy need not be explained on the basis of a direct and primary local irritation of the periphery. If lack of inhibition due to loss of control by higher centers is assumed, the primary lesion would lie in the highest centers that regulate the nutrition of the tissues. A disturbance of these centers would produce an inhibited, and therefore increased, reflex activity of the lower trophic centers and consequently would lead to atrophic changes in the tissues. This situation would be analogous to that found in the pyramidal and extrapyramidal motor systems, in which higher situated lesions produce increased reflex activity in the lower parts. Thus conceived, facial hemiatrophy would represent, so to say, a spastic paralysis of the lower trophic centers due to involvement of the higher ones.

Certain autonomic phenomena observed with lesions of the central nervous system can best be explained in this way. For instance, Kinnier Wilson regarded as a release phenomenon the profuse sweating of the feet and legs which sometimes is seen with tumors of the spinal cord. Kerr and Noble's [177] sign of increased tension of the skin below the level of a tumor of the cord, which indicates hypertonus, may best be explained as such a release phenomenon. Cannon [168] tried to apply to the autonomic nervous system Hughlings Jackson's theory of a hierarchy of functions in the central nervous system and his ideas of increased activity of the lower levels due to loss of control of the higher ones.

The present status of knowledge of the trophic influence of the nervous system (Asher,[169] Fleischhacker,[178] Goering,[143] Müller [144] and Pollak [179]) allows the assumption that high trophic centers exist in the brain, especially in the hypothalamus. Disturbances of the metabolism of fat, particularly those of hemilateral distribution (Kroll [47] and Lange [180]) observed after encephalitis epidemica, have given support to the theory of the trophic control exerted by cerebral centers. To these high cerebral centers are subordinated other centers located deeper—in the brain stem, the medulla and the spinal cord and at the periphery. A lesion at any link in this chain can produce an imbalance of the whole closely organized system of subordinated centers, an imbalance which would increase in direct proportion to the level of the lesion. According to the character, progress, extension and location of the lesion and to the status of the lower centers affected, the pathologic process set forth in the tissues may at any time come to a standstill because the lower centers may have adapted themselves to the new situation. This readjustment of the lower centers may account for the abortive and stationary forms.

Which of the numerous centers regulating nutrition of the tissues are affected in hemiatrophy? For many reasons, involvement of the highest centers of the cerebrum must be assumed. Of course, such an involvement is present in cases in which there is complete or incomplete atrophy of one half of the body. The fact might be stressed that in many cases of hemiatrophy in which apparently only the face is affected, signs of abortive involvement of other parts of the body on the same side are observed.

It is especially the concomitant features of hemiatrophy which seem to indicate cerebral involvement, the progressive facial hemiatrophy being merely a part of the general autonomic imbalance which has resulted from deranged central trophic control. Wolff and Ehrenclou [181] reported a case in which the facial hemiatrophy was combined with a disturbance of fat metabolism (lipodystrophy), a perversion of sensation, apparently of thalamic origin, and a peculiar affective state. Miskolczy and Dancz [182] reported a case of postencephalitic hemiparkinsonism combined with total hemiatrophy of the same side. In a case reported by Kirschenberg [183] hemiatrophy was accompanied homolaterally with

176. Grabs: Fall von Hemiatrophia faciei progressiva, Neurol. Centralbl. **33**:84, 1914.

177. Kerr, W. J., and Noble, C. A., Jr.: New Sign Found in Transverse Lesions of Spinal Cord, California & West. Med. **45**:346, 1936.

178. Fleischhacker, H.: Die trophischen Einflüsse des Nervensystems, in Bethe, A.; von Bergmann, G., and others: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1927, vol. 10.

179. Pollak, F.: Zur Frage der cerebralen Trophik, Arch. f. Psychiat. **89**:788, 1930.

180. Lange, W.: Wachstumsstörungen bei chronischer Encephalitis epidemica, Allg. Ztschr. f. Psychiat. **97**: 135, 1932.

181. Wolff, H. G., and Ehrenclou, A. H.: Trophic Disorders of Central Origin, J. A. M. A. **88**:991 (March 26) 1927.

182. Miskolczy, D., and Dancz, M.: Hemiatrophie mit Hemiparkinsonismus, Deutsche Ztschr. f. Nervenh. **127**:194, 1932.

183. Kirschenberg, E.: Zur Frage der Hemiatrophia faciei progressiva mit zentraler Genese, Folia neuropath. Estoniana **3-5**:94, 1925-1926.

hypalgesia, hyperesthesia for cold and hyperhidrosis. The combination of hemiatrophy with the Argyll Robertson pupil (Langelaan [184] and Surat [155]), anisocoria (Wolff [89]), acromegalic features (Wolff [89]), exophthalmos (Meyer [19]), extrapyramidal phenomena (Recht [114]), apoplexy and thalamic pain (Süss [185]) point to a central origin. A combination of hemiatrophy and homolateral hemitetany was reported by Hanse.[186] In the case of Léri [17] there was on the same side paralysis of the third to the twelfth cranial nerve, which led him to assume the presence of chronic polioencephalitis with a mesencephalic lesion of the sympathetic nervous system. Faber [187] reported that three diseases—hemiatrophy, vitiligo and myxedema—appeared in succession in the same case; he supported the view that all three disturbances were due to "an interference with the functioning of the vegetative centers in the midbrain." Cases in which the hemiatrophy is of alternating type (Bernstein,[11] Lunz,[188] Ratner [20] and Volhard [189]) clearly point to a central origin. The alopecia seen in cases of hemiatrophy can thus be easily explained (Stepp [190] and Ratner [191]). Lauerbach,[43] Mankowski,[192] Pollak,[179] Vassilevski,[23] Vivado [24] and others assumed the presence of a central lesion in cases of hemiatrophy. Its appearance after encephalitis epidemica with or without other vegetative disturbances of hemiplegic type (Kroll,[47] Mankowski,[192] Meyer,[19] Recht [114] and others) is in this respect remarkable. From his pharmacodynamic studies on patients with hemiatrophy, Bini [39] concluded that a central lesion was a more likely cause than a lesion of the cervical sympathetic trunk. Asymmetric responses from the halves of the body in pharmacologic experiments were noted by Donley,[94] Finesilver and Rosow [138] and Marinesco and associates.[148] Histologic examination in 1 case led Stief [78] to attribute hemiatrophy to disease of the opposite half of the hypothalamus.

Thus, one may conceive that hemiatrophy belongs to the release phenomena due to lack of inhibition and of normal regulation on the part of the highest trophic centers, with the consequent hypertonic and dystonic disturbances in the peripheral sympathetic trophic system.

### PROGRESSIVE FACIAL ATROPHY—A HEREDODEGENERATION

What is the nature of the primary disturbance of the highest trophic centers? Many facts indicate that it might be a pathologic condition which belongs to the vast group of developmental defects so abundant in neurology. Many names have been coined to characterize this group of chronic endogenous, autochthonous, systemic degenerations. Oppenheim spoke of congenital inferiority; Ziehen, of nuclear aplasias and dysplasias; Bing, of wearing out of a congenitally inferior system; Adler, of a congenital short span of life of single parts of the nervous system; Gowers, of abiotrophy, and Jendrassik, of heredodegeneration. Hemiatrophy may be such a heredodegeneration; it is a developmental trophic defect, a "neuronic decay," to use the expression of Kinnier Wilson's.

The course of hemiatrophy is the same as that of all other heredodegenerations. It begins in preadolescence (the statistics of Beer [62] showed that in 75.2 per cent of 109 cases the defect began before the twentieth year) and without apparent cause; it develops slowly and later becomes stationary. Patients with hemiatrophy show more pathologic conditions in their ancestry than normal persons. Among these conditions are consanguinity, epilepsy (in the case cited by Bartels [193] an uncle and a grandmother of the patient were epileptic), psychic disturbances, developmental defects and stigmas of degeneration. The mother of a patient of Léri and Weill [194] had the Marcus Gunn phenomenon. Two brothers of the father of a patient of Wahl and Christian [136] suffered from muscular dystrophy. Thomas [195] mentioned a case of facial hemiatrophy in a family affected with Friedreich's disease. Cases of hereditary and familial hemiatrophy are on record.

184. Langelaan, J. W.: Un cas d'hémiatrophie faciale avec signe d'Argyll Robertson contralatéral, Rev. neurol. **26**:520, 1913.

185. Süss, A.: Ueber eine Form halbseitiger trophischer Störungen nach einem apoplektischen Insult, Inaug. Dissert., Munich, Bottrop i W., Postberg, 1938.

186. Hanse, A.: Ueber halbseitige vegetative Störungen, Deutsche Ztschr. f. Nervenh. **102**:162, 1928.

187. Faber, K.: Facial Hemiatrophy—Vitiligo—Myxoedema, Acta med. Scandinav. **5**:419, 1934.

188. Lunz, M. A.: Hemiatrophia totalis cruciata, Deutsche med. Wchnschr. **23**:185, 1897.

189. Volhard, F.: Ueber chronische Dystrophie und Trophoneurosen der Haut im Anschluss an kasuistische Mitteilungen; Fall von Hemiatrophia facialis progressiva mit gekreuzter Pigmentation, München. med. Wchnschr. **50**:1108, 1903.

190. Stepp, C. L.: Beitrag zur Beurteilung der nach heftigen Körpererschütterungen (bes. Eisenbahnunfällen) auftretenden Störungen, Deutsche med. Wchnschr. **15**:66, 1889.

191. Ratner, T.: Alopecia universalis und Nervensystem, Deutsche Ztschr. f. Nervenh. **104**:146, 1928.

192. Mankowski: Zur Pathogenese der Hemiatrophia facialis, Arch. f. Psychiat. **78**:572, 1926.

193. Bartels: Hemiatrophia faciei, Ztschr. f. Augenh. **66**:367, 1925.

194. Léri, A., and Weill, J.: Phénomène de Marcus Gunn congénital et héréditaire, Bull. et mém. Soc. méd. d. hôp. de Paris **45**:875, 1929.

195. Thomas, A.: Héredoatrophies cérébelleuses, cerebellifuges et cérébellipétes: III. Congrès Neurologique International, Comptes rendus des Séances, Copenhagen, 1939, p. 201.

In Seeligmüller's [173] case the mother's sister was affected; in Klingmann's [6] case the grandmother, mother and twin daughters had the disease; in Raymond and Sicard's [76] case the brother and sister were affected; in the cases reported by Geist,[196] Boenheim [80] and Reiss [86] other members of the family were affected, and in Meyer's [19] case the mother's sister had the disease. The association of hemiatrophy and epilepsy has been discussed. Hemiatrophy is often associated with other degenerative diseases of the nervous system, such as psychopathy (Chasanow,[46] Donley,[94] Flint,[31] Hübner,[197] Klingmann,[6] Merritt and associates,[100] Meyer,[19] Wahl and Christian,[136] and Wolfe and Weber [28]), neuropathy (Černi,[93] Boenheim,[80] Oppenheim [29] and Krüger [120]), imbecility and underdevelopment. Beer [62] stated that 27 per cent of all patients suffering from hemiatrophy are neurotic. Cassirer [45] spoke of general inferiority and instability of the vasomotor apparatus and of the whole nervous system in these patients. In patients with hemiatrophy outspoken signs of developmental defects in other organs, such as congenital palsy of the ocular muscles, congenital hemiatrophy of the tongue, congenital facial palsy and other inherited anomalies, are often seen (Ellerbrock [198] and Harbitz [187]). Remarkable is the association of hemiatrophy with congenital torticollis (Sorsby and Shaw [199]); gigantism, eunuchoidism and acromegaly (Boenheim [80]); defect of the pectoral muscle (Kroll [47] and Chasanow [46]); heterochromia of the iris (my case 1); telangiectatic and anemic nevi (Wahl and Christian [136]); linear nevus (Tobias,[200] Marinesco and associates [148]); an anomaly of the hair whorl (Berger [201]); supernumerary nipples (Boenheim [80]); degeneration of the retina (Bini [39]), and gynandromorphism (Wolfe and Weber [28]). Instances of nonsyphilitic fixed pupil were reported (Langelaan,[184] Noïca and Vicol,[202] Oppenheim,[29] Salomon [126] and others) in which the defect was considered by some investigators as congenital. My view, expressed in a previous paper,[2] that hemiatrophy belongs to the large group of developmental defects of the nervous system, was shared by Flint [31] in the discussion of 1 of his cases:

> The suggestion, therefore, is that a congenital or inherited nervous instability is at the root of this condition and the history of this case [constitutional psychic abnormalities in the patient, her sister and her mother] certainly strengthens that suggestion.

The fact that hemiatrophy occasionally makes its appearance late in life does not speak against its heredodegenerative character. In discussing a case of hemiatrophy, Möbius [41] argued that since the symptoms appeared only at the age of 37, the patient could not have had this disease. One can hardly subscribe to his view. Marburg [42] cited a number of cases of undeniable hemiatrophy in which the symptoms appeared after the age of 30. Archambault and Fromm [1] collected from the literature cases in which the symptoms developed at ages ranging from 28 to 74 years.

The hypothesis that hemiatrophy is a cerebral heredodegeneration is supported by the argument that no adequate and plausible external cause can be found for this disease—with its slow beginning; its slow, unremitting, relentless development, and its refractoriness to treatment. As is often the case with degenerative diseases of the nervous system, the patient, to whom the idea of a spontaneous degeneration of nervous tissue is inconceivable, seeks, and usually finds, an incident that must have caused the symptoms. He often unconsciously falsifies his memories, postdates the onset and stubbornly adheres to his story. Frequently he succeeds in inveigling the physician into believing his story. A careful survey of the literature shows that there is hardly a morbid condition that has not, at some time or other, been regarded as a cause of hemiatrophy. Among the agents considered to be factors are local trauma (in 25 per cent), local infections and operations, tonsillitis, angina, extraction of teeth, alveolar abscess, exposure to cold, abscess of the ear, otorrhea, pneumonia, the forced passage of a sound down the lacrimal duct, erysipelas of the face, removal of adenoids, application of ethyl chloride spray and burns. These trivial, and in many instances very common, factors can hardly be held responsible for the development of hemiatrophy, which is one of the rarest diseases known. Trauma of the brain also is mentioned as an etiologic factor. It is hardly conceivable that any trauma could set up a system of degeneration in the depths of the brain of the slow progressive character seen in hemiatrophy.

196. Geist: Ein Fall von halbseitiger Unterentwicklung, Neurol. Centralbl. **30**:122, 1911.

197. Hübner: Bilaterale Hemiatrophia faciei, Deutsche Ztschr. f. Nervenh. **65**:26, 1920.

198. Ellerbrock, N.: Einige interessante angeborene Missbildungen, Zentralbl. f. Gynäk. **46**:898, 1922.

199. Sorsby, A., and Shaw, M.: The Refraction in Cases of Congenital Torticollis Associated with Hemiatrophy of the Face, Brit. J. Ophth. **16**:222, 1932.

200. Tobias, N.: Extensive Linear Nevus with an Associated Hemiatrophy, Arch. Dermat. & Syph. **18**: 451 (Sept.) 1928.

201. Berger, O.: Ein Fall von Hemiatrophia facialis progressiva, Deutsches Arch. f. klin. Med. **22**:432, 1878.

202. Noïca, D., and Vicol, A.: Un cas d'hémiatrophie faciale droite, Bull. Soc. méd. hôp. de Bucarest **6**:96, 1924.

Although during World War I an enormous number of head injuries occurred, now, after twenty-six years, not a single record of subsequent hemiatrophy can be found in the literature. The extensive neurologic and neurosurgical literature on head injury does not contain a single report of hemiatrophy as a result of cerebral trauma. The salient point is that in the majority of cases no external cause whatsoever can be brought into relationship with the development of the disease. Only an endogenous lesion of slowly progressive character, such as heredodegeneration, would offer an explanation for the disease. However, if a congenital developmental defect exists, say in the diencephalon, severe trauma may carry its influence into the depth of the brain and thus may accelerate, or even initiate, the disease. However, only a predisposed brain could react in this manner; never a healthy one. Severe trauma may influence the deepest parts of the brain in cases of dystrophia adiposogenitalis and of diabetes insipidus. In the same manner, trauma may influence a heredodegenerative process. Oppenheim [29] observed that an injury to the head initiated an ophthalmoplegia which was based on a congenital maldevelopment.

The assumption that peripheral trauma may influence the process of hemiatrophy is compatible with the hypothesis that this disease is due to a centrally located heredodegeneration. In a few reported cases peripheral trauma was so closely connected with the hemiatrophy, as regards both time of onset and localization, that some connection between them has to be considered. Hoffmann,[119] for instance, reported the case of a 10 year old boy who, at the age of 6, fell with the right cheek against the edge of the pavement and received a wound over the right brow. At this area a pale spot developed several months later, and little by little the right half of the face showed retardation. One is confronted here with the same problem that is presented by the influence of peripheral trauma on the development of other heredodegenerations, such as paralysis agitans or amyotrophic lateral sclerosis. Many workers, among them Kinnier Wilson, observed the beginning of amyotrophic lateral sclerosis in an area which had undergone injury. What might be the explanation? The injury is, of course, not the cause of the pathologic process. There can hardly be such a *reaction à distance* from the periphery to the brain. But hemiatrophy, considered as a heredodegeneration, has a long "incubation period." The developmental defect in the trophic centers had existed a long time before the injury occurred. When the highest trophic centers fail, the lower ones may for some time adjust themselves to the new situation and may maintain normal nutrition of the tissues. The balance of the various trophic centers had been so delicately maintained that it just provided the right trophism for the so-called passive tissues, but only under favorable external conditions. The regulation of nutrition fails when higher requirements are put on these structures after trauma. In this way the appearance of hemiatrophy in puberty can be explained, during which time, owing to the growth of the body, higher requirements are put on the trophic apparatus. Every trauma or local infection also causes irritation of the sensory tracts. The stimulus is transmitted to the vegetative system and can bring about trophic disturbances. Similar conditions prevail, for instance, in the post-traumatic bone atrophy of Sudeck. In cases of hemiatrophy, when the higher regulation and inhibition is more or less defective, the trophism is more influenced by peripheral sensory stimulation. Thus, latent hemiatrophy which is not demonstrable clinically may become apparent after trauma of the face and may then develop quickly. These changes are possible only when the central regulation has been disturbed, even in a latent or incipient form. An analogous situation may be found in those rare cases of paralysis agitans or amyotrophic lateral sclerosis in which the signs and symptoms start in an extremity that has been subjected to trauma.

Some authors attribute a role in the development of hemiatrophy to infectious disease. Most of these infections are banal and very common in children, and a connection with hemiatrophy is suggested in only a few cases. For instance, in the cases of Popova [203] and Kroll [47] hemiatrophy appeared after typhoid. When the slow hemiatrophic process is already at play, a general infection may precipitate the development of the disease. It is known that intercurrent infection may influence even such diseases as neurofibromatosis by exciting the growth of new fibromas or by causing more pigmented patches (Wilson). That heredodegeneration may develop in association with a general infectious disease is well known and has been stressed, especially by Jendrassik.[14] The congenitally weak trophic mechanism can perform its work while the organism is in good health, but it fails when higher requirements are put on it after an infection.

As heredodegeneration, hemiatrophy may be compared to other diseases based on constitu-

203. Popova, N.: Pathology and Therapy of the Hemiatrophia faciei et corporis, Sovrem. psikhonevrol. 4:475, 1927.

tional inferiority of certain centers and systems, such as narcolepsy, torsion dystonia, paralysis agitans and amyotrophic lateral sclerosis. Such a condition usually develops on the basis of an autochthonous primary systemic degeneration. This, then, is the genuine, idiopathic form of the disease. But clinically identical syndromes may be attributed to an endogenous factor. Among these factors encephalitis plays a leading role. In narcolepsy a genuine and a symptomatic form are distinguished. Torsion dystonia may develop on the basis of an autochthonous degeneration of the corpus striatum, but in some instances it is definitely postencephalitic. The same is true of paralysis agitans. Amyotrophic lateral sclerosis has been seen after encephalitis. These examples could be multiplied; they show that the same syndrome may be produced by a central lesion of particular location, regardless of its cause. Therefore it is understandable that hemiatrophy, which usually develops on a degenerative basis, may be due to some other local process, such as encephalitis. In some instances the relation to encephalitis is so close that it warrants the assumption of a causative connection between the two diseases. Reference may be made to the cases of Chasanow,[46] Kirschenberg,[183] Kroll,[47] Mankowski,[192] Meyer,[19] Recht [114] and Sterling.[204] Even in these clearcut cases of facial hemiatrophy which occurred after the onset of encephalitis, a latent, slowly progressing degeneration may have been at play. If so, the assumption would be that the patient had been born with feeble trophic centers, which were unable to withstand, in addition, the impact of a disease and that these centers suffered from it more than the other parts of the brain. In rare instances, hemiatrophy, like parkinsonism, has been attributed to arteriosclerosis (Stief [78] and Süss [185]) and to syphilis (Graff,[160] Jolly and Bassi,[205] Lewin,[206] Recht,[114] Salomon [126] and Vivado [24]). In only 1 case was it attributed to multiple sclerosis (Jolly [67]).

The apparent relationship of facial hemiatrophy to progressive lipodystrophy, which was discussed in a previous paper (Wartenberg [2]), also suggests a possible central origin. As previously stated, the atrophy of the fat tissue is the primary and dominant feature of hemiatrophy. Bilateral hemiatrophy, which is not uncommon, closely resembles lipodystrophy. In some cases of facial hemiatrophy—for instance, in my case 4—the disorder could be called unilateral facial lipodystrophy. Both diseases may, in rare instances, be hereditary. Both have complete and incomplete forms. In hemiatrophy the process transgresses the boundary of the face, while in lipodystrophy a concomitant involvement of the skin occurs. In some cases the differential diagnosis has been so difficult as to warrant a detailed discussion. The case of Wolff and Ehrenclou [181] presented features of both hemiatrophy and lipodystrophy. Many authors have stated that lipodystrophy is due to a centrally located lesion, and some assumed an underlying degenerative or encephalitic process.

The following hypothesis as to the origin of hemiatrophy, although highly speculative, may be worth mentioning. In heredodegenerative disease involving the brain there is disintegration of the highest cerebral function. In narcolepsy, for instance, a disintegration of the sleep components occurs, and in paralysis agitans there is loss of erect posture. If one assumes that a brain center or centers regulate the simultaneous and proportionate growth of both halves of the body and cement them into a compact unit, then progressive facial hemiatrophy, from the pathophysiologic standpoint, may be the first step in an attempt to dissolve this trophic unit of the organism into lateral halves. This process would be a kind of schizotrophia sagittalis. Pictures of patients with beginning or abortive hemiatrophy who have a sharply defined sagittal line of atrophy in the paramedian area seem to confirm that an attempt, so to say, is being made here to separate the body into lateral halves. Thus considered, hemiatrophy would be a disturbance of the hypothetic brain centers which integrate the lateral halves of the body and would represent a failure in the fusing function of these centers.

In order to bring some clarity into the kaleidoscopic clinical picture of facial hemiatrophy, attention has been focused on some aspects of the disease, while it has been diverted from others. There was no other way of bringing order into the maze. No hypothesis is, or ever will be, able to explain every sign and symptom in every case of hemiatrophy. Although the ideas on the pathogenesis of hemiatrophy developed in this paper have been most critically scrutinized, no definite conclusions could be established.

## SUMMARY

In cases of facial hemiatrophy, the hair of the skull and of the face is affected frequently and at an early stage. This involvement may take the form of a circumscribed alopecia or of blanching of the hair and may precede other symptoms.

204. Sterling: Hémiatrophie faciale, Rev. neurol. **34**: 138, 1927.

205. Jolly and Bassi, cited by Oppenheim.[29]

206. Lewin: Ueber die bei halbseitigen Atrophien und Hypertrophien, namentlich des Gesichtes, vorkommenden Erscheinungen, Charité-Ann. **9**:619, 1884.

The dermatologic manifestations of hemiatrophy usually start in the paramedian area of the face. This area is a vertical streak of about 1 or 2 fingerbreadths running parallel and lateral to the midline.

The existence of a disease called abortive progressive facial hemiatrophy is assumed. Its minimal atrophic changes are located in the paramedian area and become stationary for years.

So-called *sclerodermie en coup de sabre* is apparently nothing but such an abortive progressive facial hemiatrophy.

Not only hemiatrophic and sclerodermatous manifestations, but often congenital malformations of the skin, are located in the paramedian area.

The paramedian area corresponds to the vertical line of the body at which the bilateral trophic influence of the brain centers ceases and the unilateral influence begins.

The brain, especially on the affected side, often shows involvement. Contralateral epilepsy is the most conspicuous symptom of such involvement.

The fundamental manifestation of hemiatrophy is the atrophy of the fat and subcutaneous tissues.

The hemiatrophic changes may extend in various degrees from the area of the face to the homolateral parts of the body.

A patient with hemiatrophy may show, on the homolateral side of the body, abortive or latent symptoms of an atrophic process.

The pathologic process which leads directly to hemiatrophy is regarded as an active one and is due to a state of irritation in the peripheral trophic sympathetic nervous system.

In the areas of hemiatrophy, phenomena of irritation of the sympathetic, the cranial and the spinal nerves are often found. They may be explained by an irritation transmitted from the sympathetic trophic system to other systems.

Inflammatory processes are often found in the areas of hemiatrophy. They have a predilection for localization in the hemiatrophic area because the sympathetic innervation there is disturbed.

The concomitant involvement of the brain homolaterally which leads to epilepsy may be explained by disturbance of the cervical sympathetic system, which innervates the vessels of the brain. This disturbance creates a locus minoris resistentiae for toxic or infective processes.

Thus, hemiatrophy is not due to a primary inflammatory process in the peripheral sympathetic nervous system. The primary process is elsewhere, but it indirectly weakens the resistance of the affected tissues to toxi-infections.

The irritation in the peripheral sympathetic nervous system that causes hemiatrophy is a release phenomenon. It is due to disturbance of the higher centers, which leads to increased and unregulated activity of the lower centers. This phenomenon is analogous to that seen with lesions of the higher centers of the pyramidal and extrapyramidal motor systems.

The etiologic process in hemiatrophy may be encephalitis. Usually it is a heredodegeneration.

As heredodegeneration, hemiatrophy may be compared to torticollis, narcolepsy, paralysis agitans and similar diseases.

The exogenous factors that have been incriminated as causes of hemiatrophy are inadequate to explain the disease. The course of the disease is one typical of a heredodegeneration.

University of California Hospital

# LOCALIZING VALUE OF TEMPORAL CRESCENT DEFECTS IN THE VISUAL FIELDS

HENRY A. SHENKIN, M.D., AND IRVING H. LEOPOLD, M.D.
PHILADELPHIA

The fact that the most peripheral portion of the temporal field has an unpaired representation in the optic pathways and visual cortex has been well recognized. The field of the two eyes, together, or the binocular field, is the combination of the right and the left uniocular field. These partly overlap, so that the nasal field of one eye covers the greater portion, the paired portion, of the other, leaving an outer, crescentic, uniocular area unpaired. This unpaired portion is called the temporal crescent or "half-moon" (fig. 1). The paired portion has a diameter of approximately 120 degrees; the unpaired portion extends for 30 to 40 degrees on each side beyond the paired portion.

The fibers of the peripheral portion of the nasal retina pass in the medial portion of the optic nerve.[1] However, the most distal point of the visual pathway at which the fibers of the temporal crescent form a distinct and separate bundle is in the chiasm. Wilbrand's[2] study demonstrated that here they were situated ventrolaterally. These fibers from the nasal retina then pass in the most ventral portion of the tract and to the ventral portion of the lateral geniculate body.[3] According to Kronfeld,[4] there is a gap in knowledge as to the exact pathway of these "half-moon" fibers, from the external geniculate body through the subcortical area to the calcarine fissure.

Traquair[1] plotted the course in the medial portion of the optic radiation, both above and below the posterior horn of the ventricle, to end in the most anterior portion of the area striata.

Bender and Strauss[5] inferred that the fibers for vision in the temporal crescent traverse the ventral part of the optic radiations. Their conclusion was based largely on the work of Pfeiffer[6] and Poliak.[7] Pfeiffer stated the belief that all the fibers reach the cortex by passing below the posterior horn, while Polyak suggested that the calcarine fissure is reached by passing over the posterior horn as well.

Kronfeld[4] stated that the cortical representation of the temporal half-moon can exist in the lower lip of the calcarine fissure alone. However, he also asserted that the crescent may be represented above as well as below the calcarine fissure, the portion above representing the lower half, and that below the upper half, of the temporal crescent in the visual field.

It is conceivable that interference with this pathway at any point may result in a temporal crescent defect in the visual field. The studies of Traquair[8] indicated that a uniform depression of the visual field may first show a loss of the temporal half-moon. This Kronfeld[4] called a "pseudo temporal half moon." Such a finding may occur with a diffuse lesion of the optic nerve. With careful perimetric tests the inner isopters will also be found to be contracted and will thus indicate the general depression.

Lesions of the chiasm may also produce temporal crescent defects. Aneurysms of the carotid artery, tumors, anything pressing below and from the side, may catch the temporal crescent fibers. However, most changes in the fields due to lesions in the chiasmal region are bilateral;

Read at a meeting of the Philadelphia Neurological Society, Feb. 23, 1945.

From the Departments of Neurosurgery and Ophthalmology of the University of Pennsylvania.

1. Traquair, H. M.: An Introduction to Clinical Perimetry, ed. 3, St. Louis, C. V. Mosby Company, 1940, p. 74.

2. Wilbrand: Schema des Verlaufs der Sehnervenfasern durch das Chiasma, Ztschr. f. Augenh. **59**:135, 1926.

3. Brouwer, B., and Zeeman, W. P. C.: The Projection of the Retina in the Primary Optic Neuron in Monkeys, Brain **49**:1, 1926.

4. Kronfeld, P. C.: The Temporal Half Moon, Tr. Am. Ophth. Soc. **30**:43, 1932.

5. Bender, H. B., and Strauss, I.: Defects in Visual Field of One Eye Only in Patient with a Lesion of One Optic Radiation, Arch. Ophth. **17**:765, (May) 1937.

6. Pfeiffer, R. A., in Schieck, F., and Brückner, A.: Kurzes Handbuch der Ophthalmologie, Berlin, Julius Springer, 1930, vol. 1, p. 426.

7. Poliak, S.: The Main Afferent Fiber Systems of the Cerebral Cortex in Primates, Berkeley, Calif., University of California Press, 1932, vol. 2, p. 370.

8. Traquair, H. M.: Essential Considerations in Regard to the Field of Vision; Contraction or Depression? Brit. J. Ophth. **8**:49, 1924.

in addition, careful perimetric studies in a case of pituitary tumor may often show hemichromatopsia, even in the early stages, which will aid in localizing the lesion. Although the occurrence of a unilateral cut in the temporal crescent due to a lesion in the region of the chiasm is conceivable, it is not likely, as the fibers in this region are too compact. Also,

Lesions above the external geniculate body can produce a uniocular temporal crescent defect in the visual field by involving the radiations in the temporoparieto-occipital area or the anterior tip of the visual cortex itself.

Lutz [9] reported several cases in which a defect existed only in the uniocular field of vision. Behr [10] observed several cases in which at cer

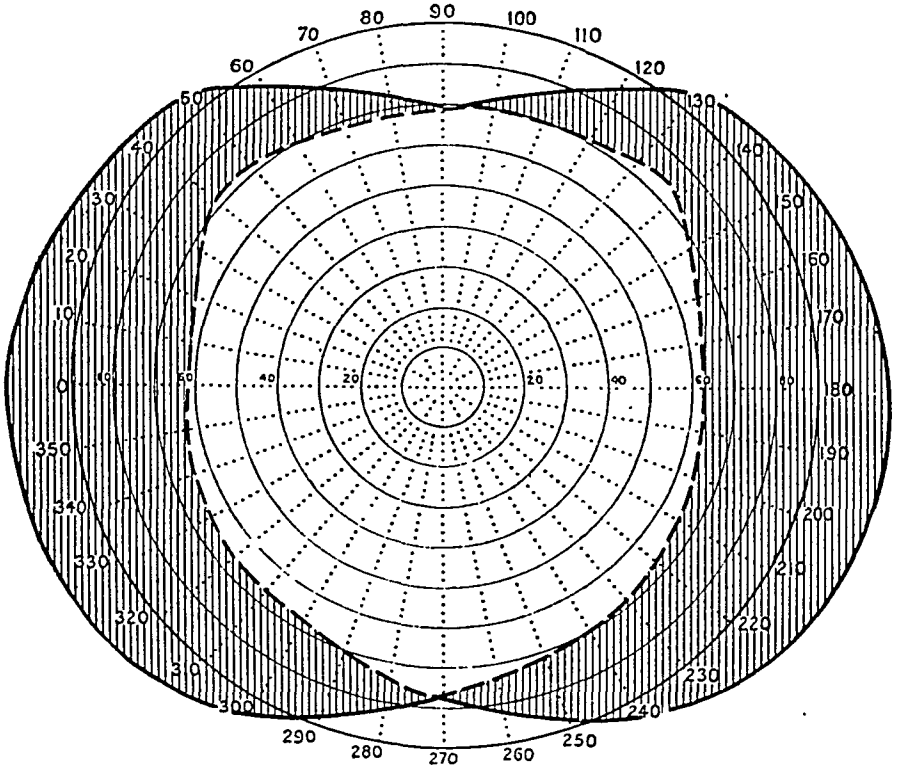



Fig. 1.—The binocular field, showing the crescentic unpaired areas (taken from Traquair [1]).

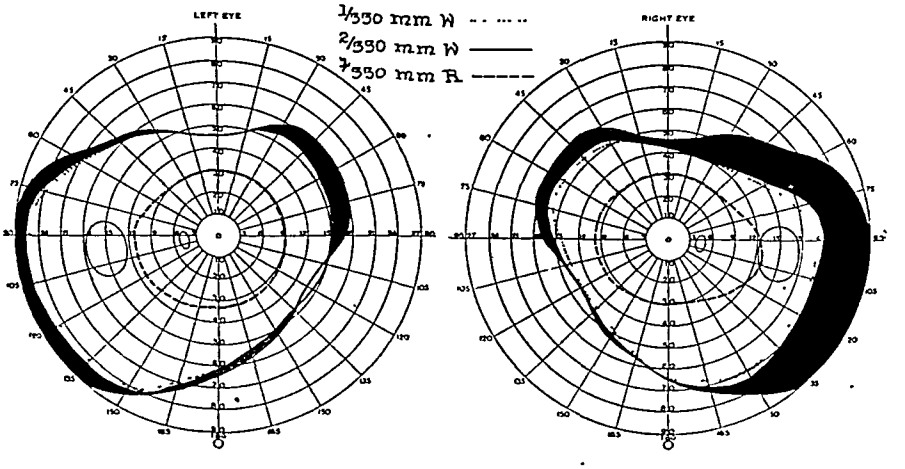



Fig. 2 (case 1).—Perimetric fields taken April 8, 1928, wtih vision of 6/9 in each eye.

central vision would most likely be involved by a lesion in this area because of the proximity of the macular fibers. Kronfeld [4] could find no proved cases in the literature of isolated unilateral defects of the temporal half-moon from lesions of the chiasma or the optic tract.

9. Lutz, A.: Ueber asymmetrische homonyme Hemianopsie und Hemiakinesis pupillaris, Arch. f. Ophtl **116**:186, 1925.

10. Behr, C.: Die homonymen Hemianopsien mi einseitigem Gesichtsfelddefekt im "rein temporalen halb mondförmigen Bezirk des binokularen Gesichtsfeldes, Klin. Monatsbl. f. Augenh. **56**:161, 1916.

tain stages of disease of the central visual tract a defect in the uniocular temporal crescent was present alone.

Kronfeld [4] presented 26 cases from the literature and 3 of his own, demonstrating various lesions in which the temporal crescents were of

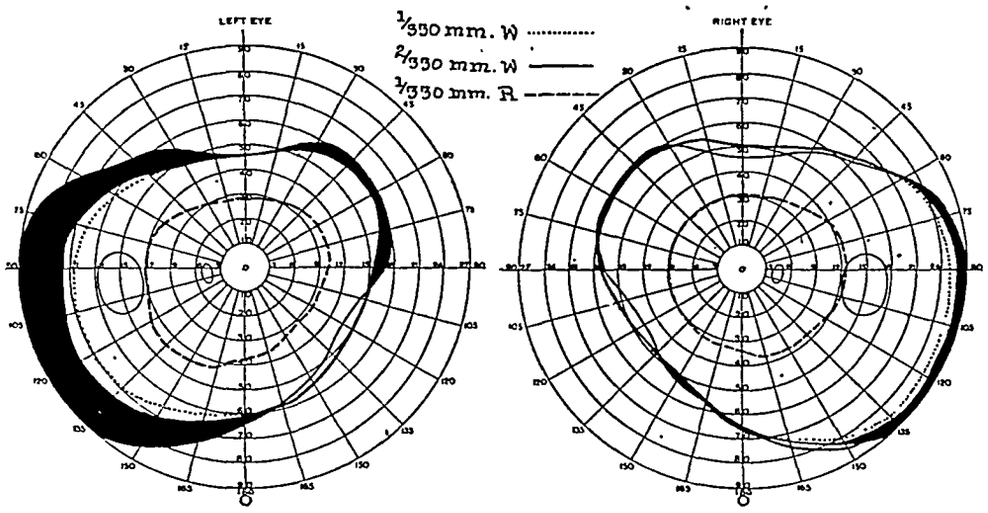



Fig. 3 (case 2).—Perimetric fields, with vision of 6/6 in each eye.

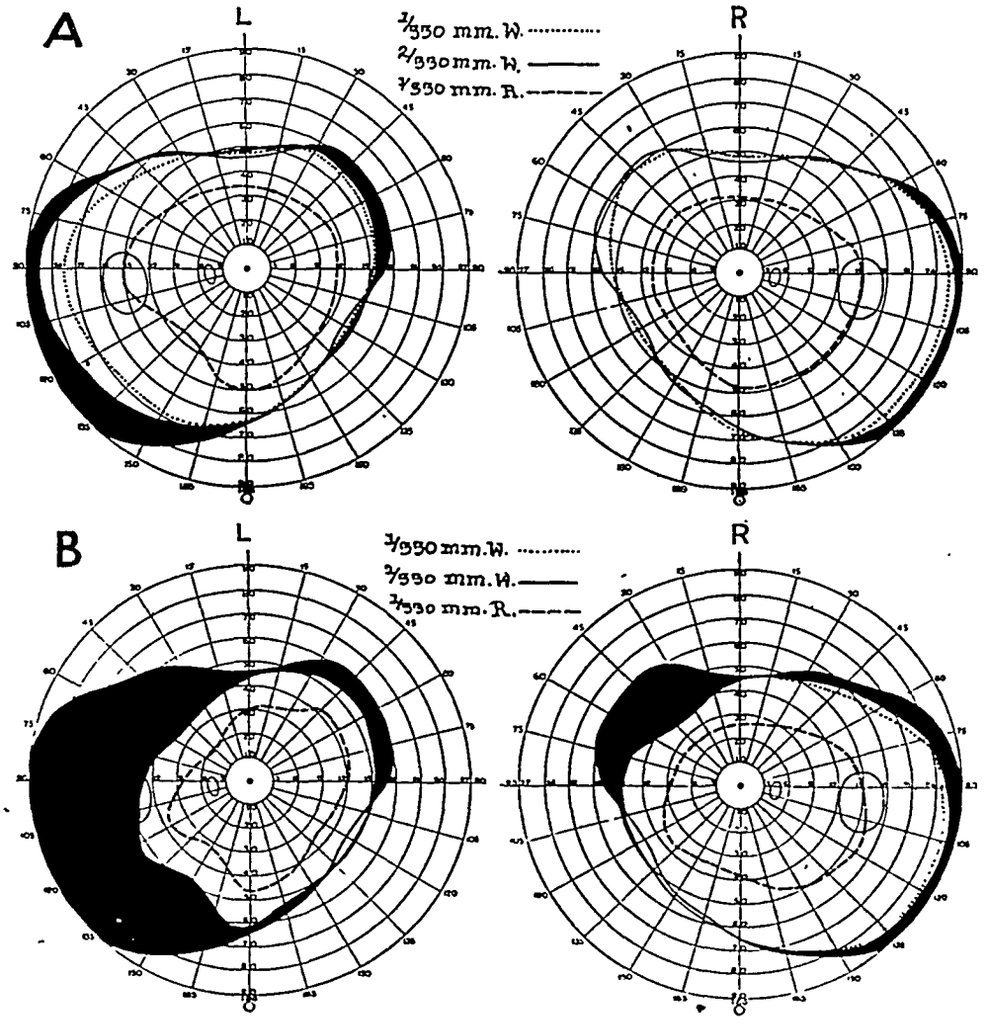



Fig. 4 (case 3).—Perimetric fields taken (*A*) before operation and (*B*) two months later.

importance either by their absence or by their presence.

Bender and Strauss [5] reported 10 cases in which, as a result of lesions of the optic radiations, an unpaired crescentic or hemicrescentic defect existed in the periphery of the temporal field of vision. They concluded that an unpaired peripheral scotoma indicates an early defect in the optic radiations and that such a finding has localizing value in the early diagnosis of tumor of the brain.

It is the purpose of this paper to substantiate these observations of Bender and Strauss with 5 verified cases of brain tumor and to emphasize the value of this sign as an aid in the practical localization of a pathologic cerebral process.

REPORT OF CASES

CASE 1.—G. J. Mc., a 43 year old minister, complained of numerous "nervous breakdowns" over a period of five years. An automobile accident, two years prior to operation, in which the patient suffered a minor cranial trauma, occasioned a roentgenographic examination of his skull, which showed "thickening of bone of the left parietal region." Eight months before admission he had a generalized convulsion, from which he completely recovered. However, seven months after this convulsion severe headaches developed, which were soon followed by projectile vomiting and blurred vision. Neurologic examination on admission revealed that the patient was drowsy; but though his reaction time was considerably slowed, he responded intelligently to questions. The respiratory rate on occasions fell to 12 per minute. A decided lump could be palpated over the left parietal region. Neurologic examination revealed nothing significant save for some weakness of the left hand and a Babinski sign on the left side. Visual acuity was 6/9 in each eye without correction. Ophthalmoscopic examination revealed normal optic nerve heads. Perimetric studies showed a distinct crescentic cut in the right field of vision, without any changes in the central field (fig. 2). Roentgenographic studies gave evidence of atrophy of the dorsum sellae and an area of hyperostosis of the left parietal region. Operation at the site of the hyperostosis revealed a large meningioma in the left parieto-occipital region.

CASE 2.—M. B., a 35 year old woman, complained of headache of one year's duration and vertigo with change of position for six months. She had had progressiv left hemiparesis and recurrent sensory jacksonia seizures on the left side for six months. Neurologi examination revealed spastic left hemiparesis and im paired sense of position of the left large toe and thumt There were a Babinski sign and ankle clonus on th same side. Roentgenograms of the skull showed atroph of the dorsum sellae. The spinal fluid pressure wa normal. Ophthalmoscopic examination disclosed papil ledema of about 1 D. in each eye. Visual acuity wa 6/6 in each eye without correction. Perimetric studies revealed a crescentic cut in the left visual field. The peripheral field of the right eye was full, and no changes were detected in the central field of either eye (fig. 3). Operation disclosed a large meningioma of the right parietal region.

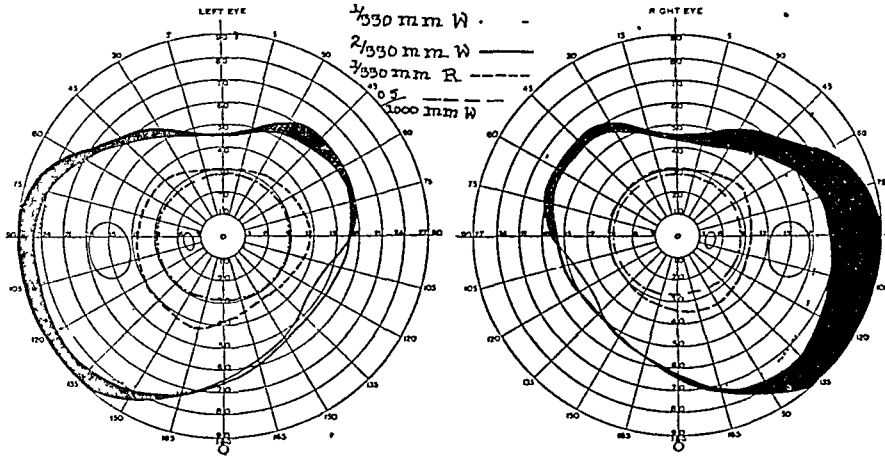



Fig. 5 (case 4).—Perimetric fields, with vision of 6/6 in each eye.

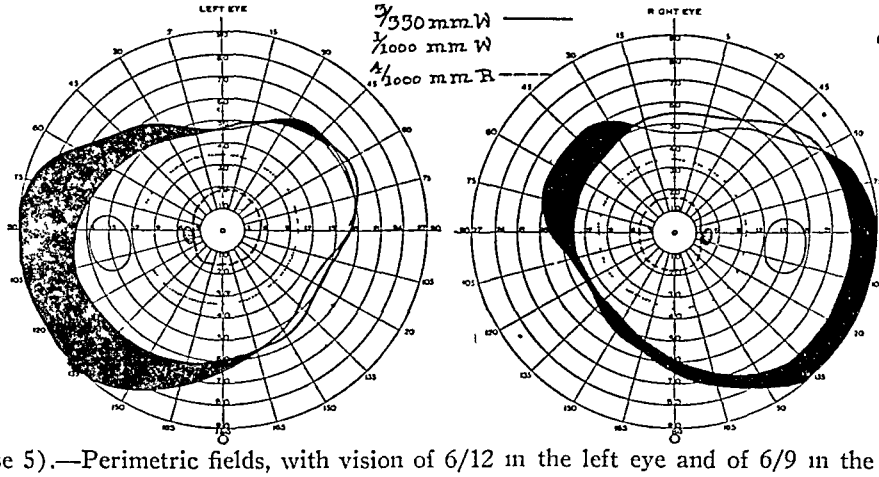



Fig. 6 (case 5).—Perimetric fields, with vision of 6/12 in the left eye and of 6/9 in the right eye.

CASE 3.—M. F., a 22 year old woman, had had headaches for eight months, together with seizures consisting of opisthotonos and exacerbations of headache. The results of neurologic examination were essentially negative. Roentgenograms of the skull revealed calcification deep within the right parieto-occipital area. The optic disks were slightly blurred, but no measurable elevation of the margins existed. Visual acuity was 6/6 in each eye without correction. Determination of the visual fields revealed only a temporal crescent cut in the left visual field, without changes in the central field in either eye (fig. 4 *A*). The operation was done in two stages. In the first procedure, a bone flap was turned down in the parieto-occipital region but the dura was not opened. Perimetric examination performed four weeks after the first surgical procedure showed an incongruous left homonymous hemianopsia (fig. 4 *B*). Subsequently the tumor

was exposed and proved to be a well demarcated cystic astrocytoma deep in the right parieto-occipital region.

CASE 4.—J. L. W., a 57 year old man, had shown personality changes for six months and progressive aphasia for four months. He had had weakness of his right hand for four weeks and weakness of his right leg for two weeks. Neurologic examination showed right hemiparesis, most marked in the upper extremity, together with hyperreflexia, a Babinski sign and ankle clonus, all on the right side. There were distinct hypesthesia and hypalgesia on the same side. Astereognosis was present in the right hand. The position sense in the right large toe and the right hand was notably impaired. His aphasia appeared to be predominantly of the sensory type. Roentgenograms of the skull and the ocular fundi were normal. Visual acuity was 6/6 in each eye with correction. Determination of the visual fields disclosed a temporal crescent defect in the right visual field (fig. 5). Operation revealed a large cystic glioma of the left parietal area.

CASE 5.—I. M., a 51 year old man, had been drowsy for one month. Headache was said to be of only one week's duration, but he had had a progressive left hemiparesis for one month. He was admitted to the hospital, after having been comatose for twenty-four hours. Examination on admission disclosed spasticity of all four extremities, a stiff neck and a positive Babinski sign on the left side. Ophthalmologic examination had been done three weeks prior to admission and revealed a visual acuity of 6/9 in the right eye and 6/12 in the left eye without correction. The fundi were normal. Determination of the visual fields at this time revealed the temporal crescent defect in the left visual field and no sign of changes in the central field (fig. 6). Operation exposed a glioblastoma multiforme of the right temporoparietal area.

### COMMENT

These cases are presented to emphasize that careful perimetric studies may reveal a defect in one unpaired portion of the visual field, i. e., the temporal crescent, which is of practical importance to the neurologist and the neurosurgeon. A uniocular crescent defect would indicate the laterality and general area involved by a tumor or other pathologic process.

No exact anatomic information may be derived from these cases. The position of the tumor itself may not tell the entire story, for cerebral tumors produce edema and other distant reactive phenomena which may also cause disturbances in the fields of vision. However, in all these 5 cases the supragenicular pathways and, more definitely, the ventromedial portion of the radiations in the parietal, temporoparietal and parieto-occipital areas were involved.

A unilateral temporal crescent defect alone is not a common finding. The incidence reported by Bender and Strauss in 100 cases of verified tumors in which the fields could be plotted was 10 per cent. Several hundred of the neurosurgical records of Dr. Charles H. Frazier and Dr. Francis C. Grant had to be searched before finding these 5 cases. The vast majority of the tumors involving the optic radiation show further advanced changes in the visual fields, such as homonymous hemianopsia. A uniocular crescent cut is usually disregarded. Case 3 beautifully demonstrates the advance from a unilateral crescent cut to bilateral involvement of the field, toward a homonymous hemianopsia. Bender and Strauss have previously noted that, irrespective of the location of the lesion in the optic radiation, homonymous anopsias usually begin in the periphery and advance toward the center. This brings out the importance of the temporal crescent defect as an early localizing sign.

### SUMMARY

In 5 cases presented here, uniocular temporal crescent defects in the visual field were due to verified cerebral tumors involving the supragenicular pathway. This finding is important as an early localizing sign.

### DISCUSSION

DR. JOSEPH C. YASKIN, Philadelphia: The chief value of this contribution is that the presence of the temporal crescent defect in the absence of a nasal defect on the opposite side should arouse suspicion of the involvement of the contralateral visual pathways behind the primary visual centers. I am surprised that so few examples of this sign were found in the large collection of cases of tumor. I should like the authors to state how frequently this defect is observed in cases of chiasmal syndromes to which they alluded.

The authors' observations on small defects of the temporal field are valuable when these defects are found to be constant by repeated studies.

DR. HENRY SHENKIN, Philadelphia: Dr. Yaskin asked about chiasmal lesions. I have no doubt that they occur frequently; however, since the chiasmal fibers are so compact, defects due to lesions of the chiasma will tend to be bilateral, not unilateral.

Kronfeld was unable to find in the literature a case of a unilateral crescent defect due to a chiasmal lesion. Kronfeld's paper appeared in 1932, and no such case has since been reported.

These defects are often overlooked. I think that a 5 degree difference between the two fields should be regarded as significant.

Hospital of the University of Pennsylvania.

# DEGENERATION OF PERIPHERAL NERVES IN PERNICIOUS ANEMIA

LIEUTENANT D. BERNARD FOSTER
MEDICAL CORPS, ARMY OF THE UNITED STATES

The signs and symptoms of disease of the peripheral nerves associated with pernicious anemia and subacute combined degeneration have been noted by a number of observers, estimates of the incidence varying from 4.9 [1] to 23 [2] per cent. The separation of neuritic from myelitic components in a diffuse disease of the nervous system is notoriously difficult and unreliable, and for this reason the status of the peripheral nerves in this disorder has been speculative and controversial. Since peripheral nerves have a powerful regenerative capacity as compared with the insignificant recuperative powers of the central nervous system, the presence and degree of neuritic damage in pernicious anemia are important in prognosis and therapy. This report describes the pathologic changes in the peripheral nerves in 4 cases in which autopsy was performed and the results of biopsy of a peripheral nerve in an additional case.

## REPORT OF CASES

CASE 1.—N. B., a 66 year old white woman, was found elsewhere to have pernicious anemia in 1928 and was treated with oral and parenteral administrations of liver extract until 1941, when she discontinued all treatment. Anorexia, alternating diarrhea and constipation, weakness and intellectual impairment appeared and progressed insidiously in the twenty-five month period between cessation of therapy and her admission to University Hospital.

The patient was pale, cachectic, dehydrated and in a severe confusional state. The knee and achilles jerks were absent, and there was a bilateral extensor plantar response. Vibratory sensation and the sense of position were absent in the lower extremities, and she was incontinent of urine and stool. The hemoglobin of the blood measured 3.2 Gm. per hundred cubic centimeters; the red cell count was 600,000 and the white cell count 2,250 per cubic millimeter, and the mean corpuscular volume of the red blood cells was 133 cubic microns.

Transfusions and parenteral administration of liver extract were begun, but pneumonia resulted in death seven days after her admission to the hospital, and fifteen years after onset of the disease.

Pathologic examination showed acute purulent bronchitis, lobular pneumonia and advanced chronic atrophic gastritis. Bone marrow from a rib, the sternum and a vertebral body had a cellular content averaging 90 per cent and contained numerous immature cells and megakaryocytes.

The brain was not examined. The spinal cord showed demyelination, vacuolation and gliosis in the gracile component of the posterior column and gliosis in the intramedullary course of the entering posterior root fibers (fig. 1); the cuneate component of the posterior column and the lateral columns presented similar changes of minimal degree. There was a diffuse increase in Marchi globules, most marked in the posterior columns and in the intramedullary course of the posterior root fibers. Nissl's chronic cell disease was present in numerous anterior horn cells, which showed corkscrew dendrites, pyknosis and poor or no differentiation between nucleus and cytoplasm.

About 25 per cent of the ganglion cells of the posterior root ganglia (lumbosacral segments) were normal (fig. 2). The remainder showed varying degrees of degenerative change, ranging from fraying of the cell margins, vacuolar cell change and reduction of Nissl substance to fine, dustlike particles, to complete dissolution of the cell and its replacement by proliferated capsular cells and connective tissue. Mild Marchi degeneration was present in segments of the brachial plexus, and the femoral nerve showed a pronounced distortion of myelin sheaths and increase in Marchi globules. Sections of the posterior roots and the femoral nerve stained with azocarmine showed hypertrophy and hyperplasia of the Schwann cells, reduction in myelin sheaths and axis-cylinders and a substantial increase in the endoneurial connective tissue.

CASE 2.—A. G., a 67 year old lumberman, was admitted to University Hospital because of complete paralysis of the lower extremities, of six months' duration. His neurologic symptoms were of fifteen years' standing and had begun with numbness and tingling in the hands and feet. Weakness and ataxia had been intermittent during this period; an exacerbation of this weakness and unsteadiness in the legs had begun twelve months prior to his admission, and he had been bedfast for six months prior to examination at this hospital.

He presented a simple organic dementia. The upper extremities were paretic, atrophic and ataxic, and the biceps and triceps reflexes were diminished. There was complete paraplegia in flexion with bilateral foot drop in the lower extremities, accompanied with secondary joint contractures at the hips and knees; muscular tone was increased, and there was moderate atrophy. The knee and achilles jerks were absent, and there was a bilateral Rossolimo sign but no extensor plantar response. Sense of position and vibratory sensation were absent in the lower extremities, and superficial

From the Department of Neurology and the Neuropathology Laboratory of the Neuropsychiatric Institute, the University Hospital and the University of Michigan Medical School.

1. Woltman, H. W.: The Nervous Symptoms in Pernicious Anemia, Am. J. M. Sc. **157**:400-409, 1919.

2. Dynes, J. B., and Norcross, J. W.: Peripheral Neuritis as a Complication of Pernicious Anemia, J. A. M. A. **122**:586-588 (June 26) 1943.

sensation was diminished below the knees. He was incontinent of urine and stool. Physical and roentgenographic signs of pulmonary tuberculosis were likewise present. The hemoglobin of the blood measured 7.7 Gm.; the red cell count was 2,000,000 and the white cell count 3,050 per cubic millimeter, and the mean corpuscular volume of the red blood cells was 120 cubic microns. There was complete gastric achlorhydria.

Parenteral injections of liver extract produced improvement in the blood values, but death resulted from pulmonary tuberculosis one and a half months after his admission.

Pathologic examination showed tuberculous cavitation in the left lung; epithelioid tubercles in the spleen, liver and bronchial lymph nodes; atrophic gastritis, and chronic cholecystitis with cholelithiasis. Bone marrow

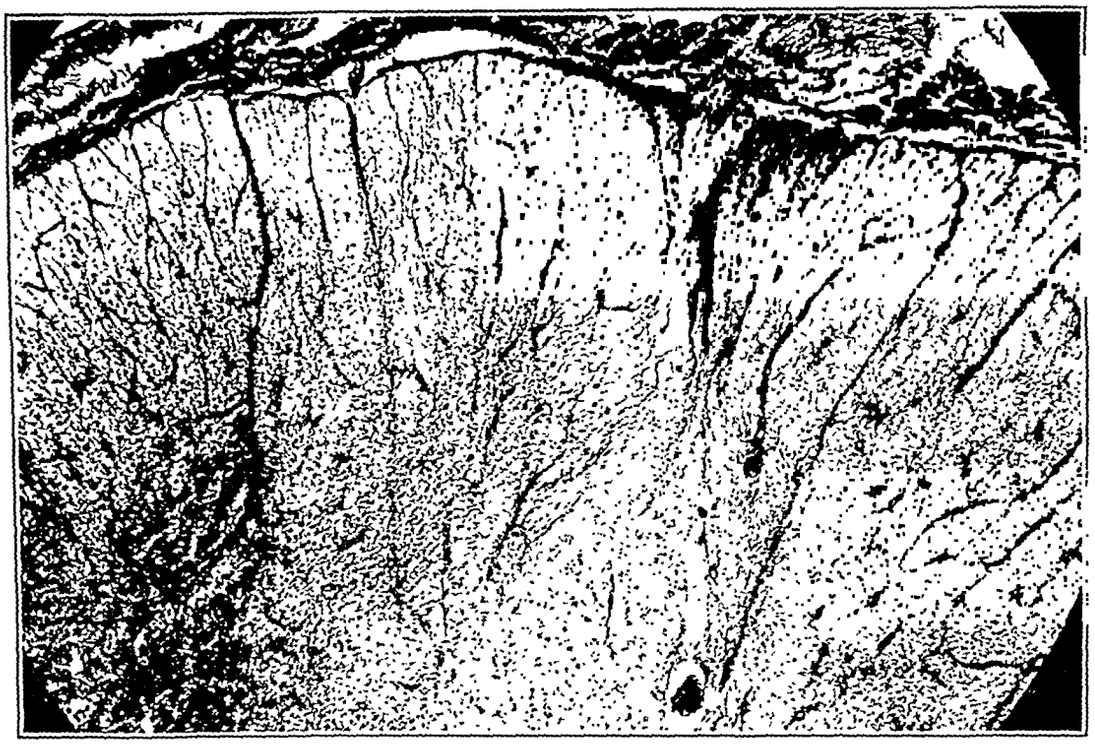


Fig. 1 (case 1).—Severe gliosis in the gracile component of the posterior column of the middorsal portion of the cord (at left) and increase in glia fibers in the course of the intramedullary fibers of the posterior root (upper right portion). Holzer stain for glia fibers; Zeiss planar lens 20 mm.

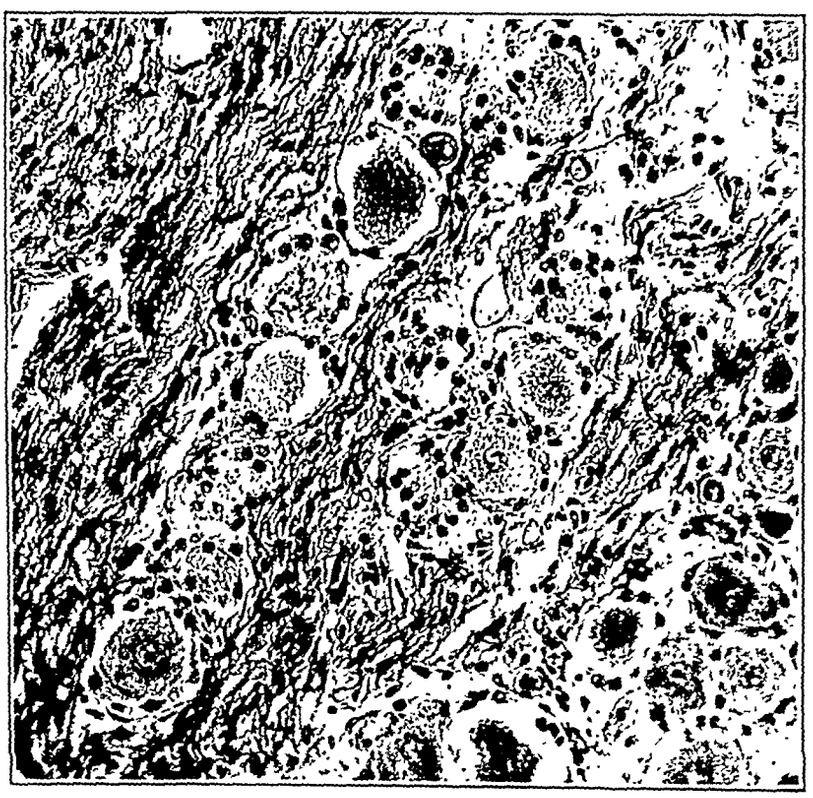


Fig. 2 (case 1).—Regressive changes in the posterior root ganglion of a lumbar segment: pyknosis, neuronophagia and replacement of ganglion cells by proliferations of capsular cells. Azocarmine stain; Zeiss planar lens 20 mm., ocular 2.

from a rib, the sternum and a vertebral body had a cellular content averaging 50 per cent and contained numerous megakaryocytes.

matter (fig. 3), for the most part perivascular, although this relationship was not always apparent; the Holzer stain for glia fibers demonstrated fine, radiating glia

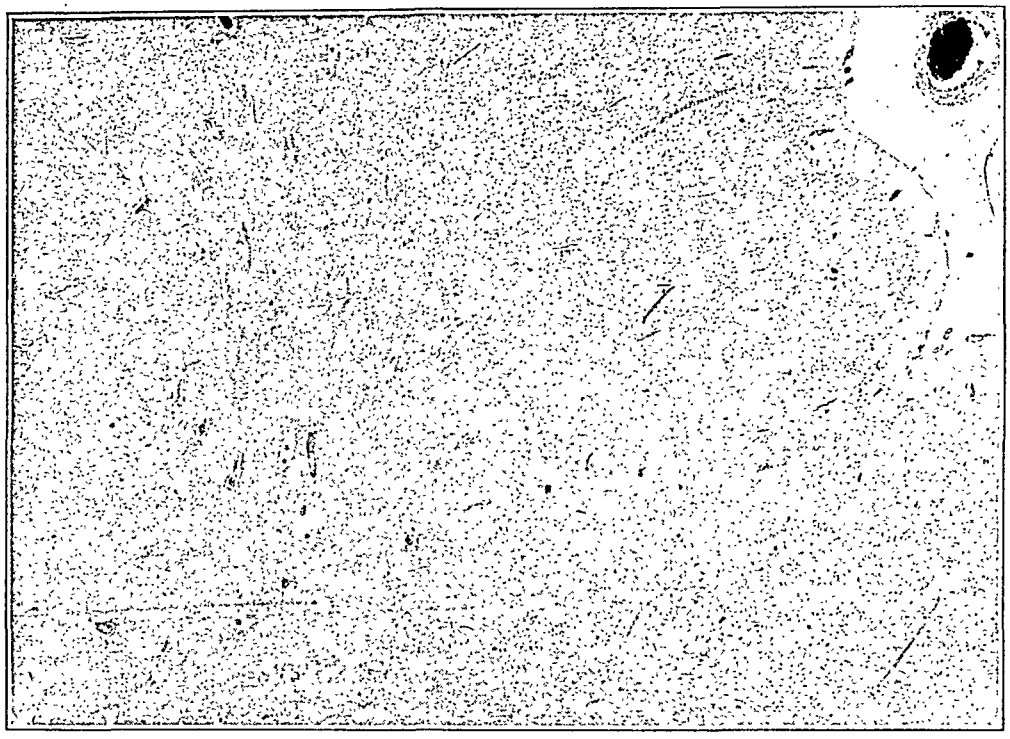


Fig. 3 (case 2).—Areas of perivascular demyelination in the subcortical white matter of the frontal lobe. Hematoxylin and eosin stain; Zeiss planar lens 20 mm.

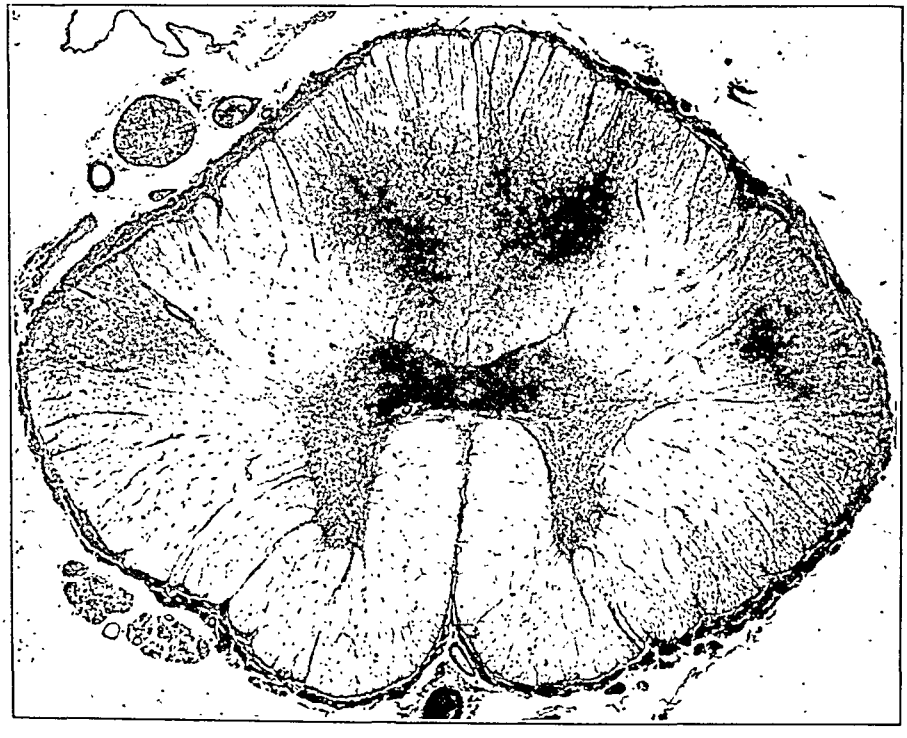


Fig. 4 (case 2).—Increase in glia fibers in the posterior and lateral columns of the middorsal portion of the cord, with vacuolation in the same areas; gliosis in the gray matter, particularly around the central canal, and increase in glia fibers in the intramedullary fibers of the right posterior root. Neurologic symptoms had existed for fifteen years; no liver treatment had been given until one and a half months before death. Compare with figure 7. Holzer stain for glia fibers; Zeiss planar lens 50 mm.

There were no signs of tuberculosis in the nervous system. Numerous areas of rarefaction and demyelination were distributed throughout the subcortical white fibers from the blood vessels in the areas of demyelination. No abnormalities were found in the basal ganglia or the brain stem. There were advanced gliosis

and vacuolization in the posterior columns of the spinal cord, with less severe changes in the lateral columns (fig. 4). Glia fibers were diffusely increased throughout the gray matter, being of greatest density around the central canal. Numerous Marchi globules followed the course of entering posterior root fibers. The ventral horn cells were well preserved.

Azocarmine preparations of the femoral and sciatic nerves showed loss of myelin and axis-cylinders and proliferation of Schwann cells, of lesser severity than in case 1.

CASE 3.—A. H., a 56 year old white woman, had had remissions and exacerbations of weakness, ataxia and

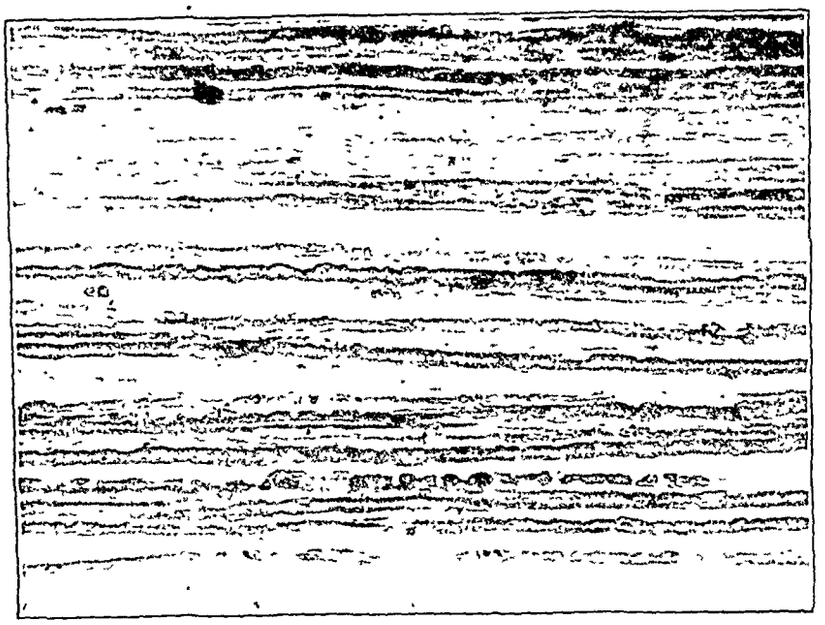


Fig. 5 (case 2).—Beaded, tortuous myelin sheaths and formation of Marchi globules in the superficial peroneal nerve. Marchi stain; Zeiss planar lens 20 mm., ocular 2.

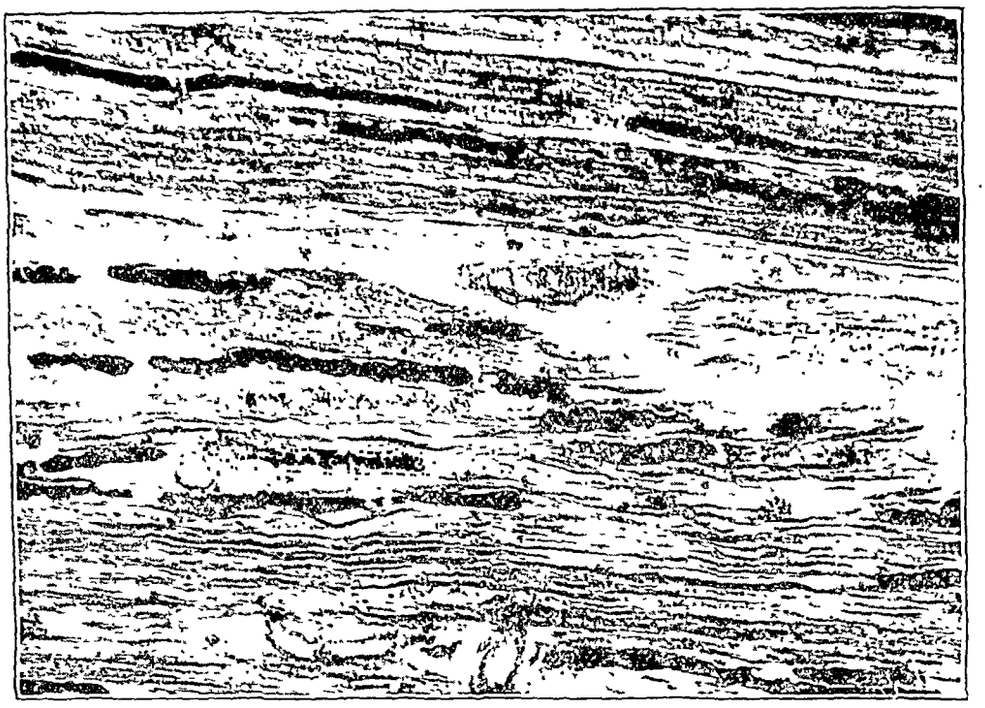


Fig. 6 (case 3).—Numerous intracellular, extracellular and perivascular Marchi globules in the superficial peroneal nerve. Marchi stain counterstained with azocarmine; Zeiss planar lens 20 mm., ocular 2.

Approximately 35 per cent of the ganglion cells of the posterior root ganglia in the lumbosacral segments were normal, the others showing degenerative cellular changes and proliferation of the capsular cells, as in case 1. Minimal Marchi degeneration was present in the nerve fibers of the brachial plexus, moderately severe changes in the femoral nerve and advanced Marchi degeneration in the superficial peroneal nerve (fig. 5).

inability to walk for twenty-four years. She had been confined to bed for the preceding eight months with headache, anorexia, increasing paralysis of the lower extremities, intermittent incontinence of urine and stool and progressive edema.

On admission to University Hospital, she was acutely ill and cachectic, with peripheral edema to the sacrum, ascites and a distended bladder. There were mild intel-

lectual loss; bilateral nerve deafness; spasticity, paresis, ataxia and atrophy in the upper and lower extremities, and hyperactive deep tendon reflexes bilaterally, with the Hoffmann sign, an extensor plantar response and ankle clonus on both sides. The sense of position and vibratory sensation were absent in the lower extremities and diminished in the upper extremities, and there were severe distal hypasthesia and hypalgesia in the lower extremities. The hemoglobin of the blood measured 3.5 Gm.; the red cell count was 900,000 and the white cell count 1,350 per cubic millimeter, and the mean corpuscular volume of the red blood cells was 111 cubic microns. There was complete achlorhydria. A series of grand mal convulsions occurred on the third and fourth hospital days but none thereafter.

With transfusions, parenteral administration of liver extract and large doses of vitamin preparations, there was considerable general improvement, and the blood values returned to normal.

A biopsy specimen of the superficial peroneal nerve (fig. 6) was taken forty days after treatment was begun. Marchi sections counterstained with the azocarmine technic showed marked tortuosity, swelling and distortion of the myelin sheaths and numerous Marchi globules from degenerating myelin. The endoneurial connective tissue was increased, and Schwann cells were abundant. The few remaining axis-cylinders showed extensive disintegration.

CASE 4.—C. O., a 58 year old real estate dealer, had the onset of numbness and tingling in the hands and feet fifteen months before the initial examination at University Hospital. This was followed by generalized weakness and ease of fatigue, sensations of walking on cotton, vesical incontinence and a weak, staggering gait, which progressed to complete inability to stand without support.

There were gross paresis and ataxia in the lower extremities. The knee and achilles jerks were absent, and there was a bilateral extensor plantar response. Vibratory sensation and the sense of position were diminished in the lower extremities; the bladder was distended. There was no free acid in the gastric contents; the hemoglobin of the blood measured 7 Gm.; the red cell count was 2,040,000 and the white cell count 6,800 per cubic millimeter, and the Price-Jones curve was shifted to the right. Parenteral administration of liver extract produced a satisfactory reticulocyte response.

When the patient was reexamined three years later, the blood values were normal. He walked with a mildly ataxic gait; the biceps, triceps, patellar and achilles reflexes were hyperactive; the plantar responses were extensor, and there was bilateral ankle clonus. Vibratory sensation was diminished in the lower extremities, and the sense of position was intact. The incontinence had disappeared.

He was not seen again in University Hospital until fifteen years after his initial symptoms. He had maintained oral liver therapy regularly and had been able to do light work, but the blood values for this intervening period were not known. He was admitted to the hospital in coma, with severe congestive heart failure of two weeks' duration, manifested by cardiac enlargement, auricular fibrillation, edema of the lungs, ascites and peripheral edema to the sacrum. The hemoglobin of the blood was 16.2 Gm.; the red cell count 5,100,000 per cubic millimeter, and the mean corpuscular volume of the red blood cells was 103 cubic microns. He failed to improve with administration of oxygen, digitalis and mercurophylline and died three days after admission.

Pathologic examination showed old and recent myocardial infarctions; ventricular thrombi with infarctions in the lungs, kidneys and liver; congestion of all viscera, and anasarca. Bone marrow from a vertebral body, a rib and the sternum showed congestion and a cellular content averaging 80 per cent.

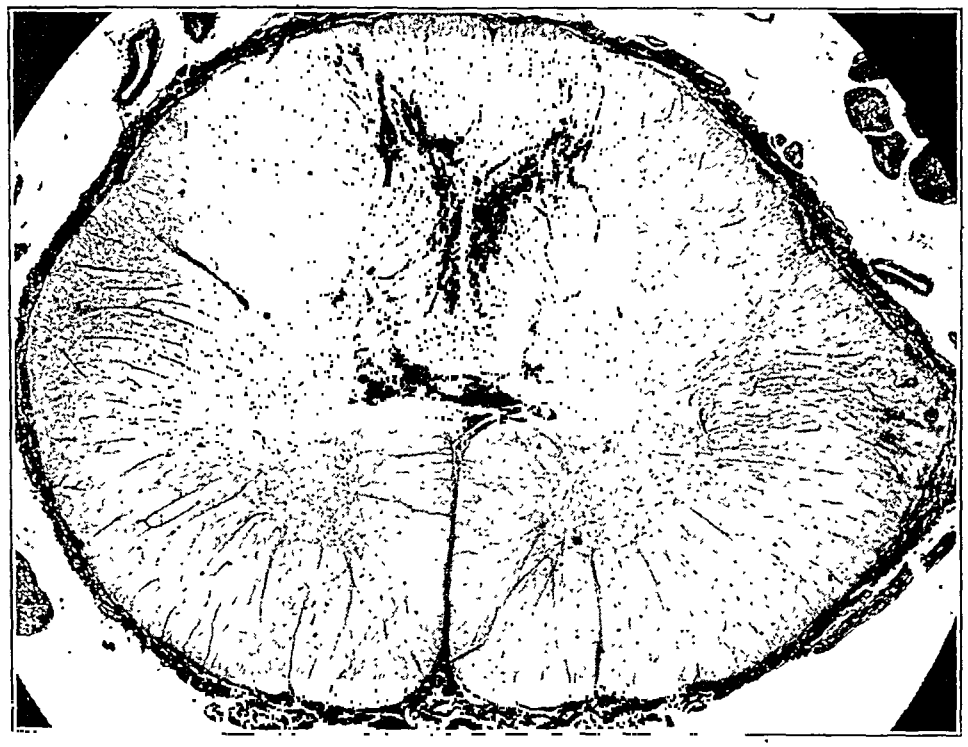


Fig. 7 (case 5).—Gliosis in the posterior column, the lateral column and around the central canal in the high dorsal portion of the cord. Liver therapy was begun fifteen months after onset of neurologic symptoms and was continued until death, fifteen years later. Holzer stain for glia fibers; Zeiss planar lens 50 mm.

The spinal cord (fig. 7) showed mild vacuolation and gliosis in the gracile component of the posterior column; there was minimal gliosis in the lateral columns. A mild increase in glia fibers was present in the entering fibers of the posterior roots. Marchi globules were infrequent in the spinal cord; none were found in the intramedullary course of the posterior roots. The ventral horn cells were well preserved, and the gray matter was normal except for a mild increase in glia fibers about the central canal. About 40 per cent of the ganglion cells of the posterior root ganglia of the lumbosacral portion of the cord were normal, the remainder showing fraying of the cell margins, swelling of the nuclei, diminution or absence of tigroid substance, vacuolar degeneration or complete degeneration, with invasion of the ganglion cell space by capsular cells. There was increased connective tissue within the ganglia and in the posterior roots. Marchi degeneration of mild degree was present in the sciatic and femoral nerves; the reticulocyte response followed the parenteral administration of liver extract.

The blood values were maintained within normal limits during the ensuing eleven years with a preparation of powdered stomach and parenteral administration of liver extract. The patient no longer worked as a printer after treatment was begun. He was admitted to the hospital in 1943 because of severe gastrointestinal symptoms, which proved on examination to be due to carcinoma of the stomach, with metastases to the liver. At this time the biceps, triceps and patellar reflexes were diminished; the achilles reflexes were absent, and there was a doubtful extensor plantar response on the right side. Vibratory sensation was diminished but present at the ankles; the sense of position was intact in the toes. The hemoglobin of the blood measured 10.3 Gm.; the red cells numbered 4,000,000 per cubic millimeter, and the mean corpuscular volume of the red blood cells was 80 cubic microns.

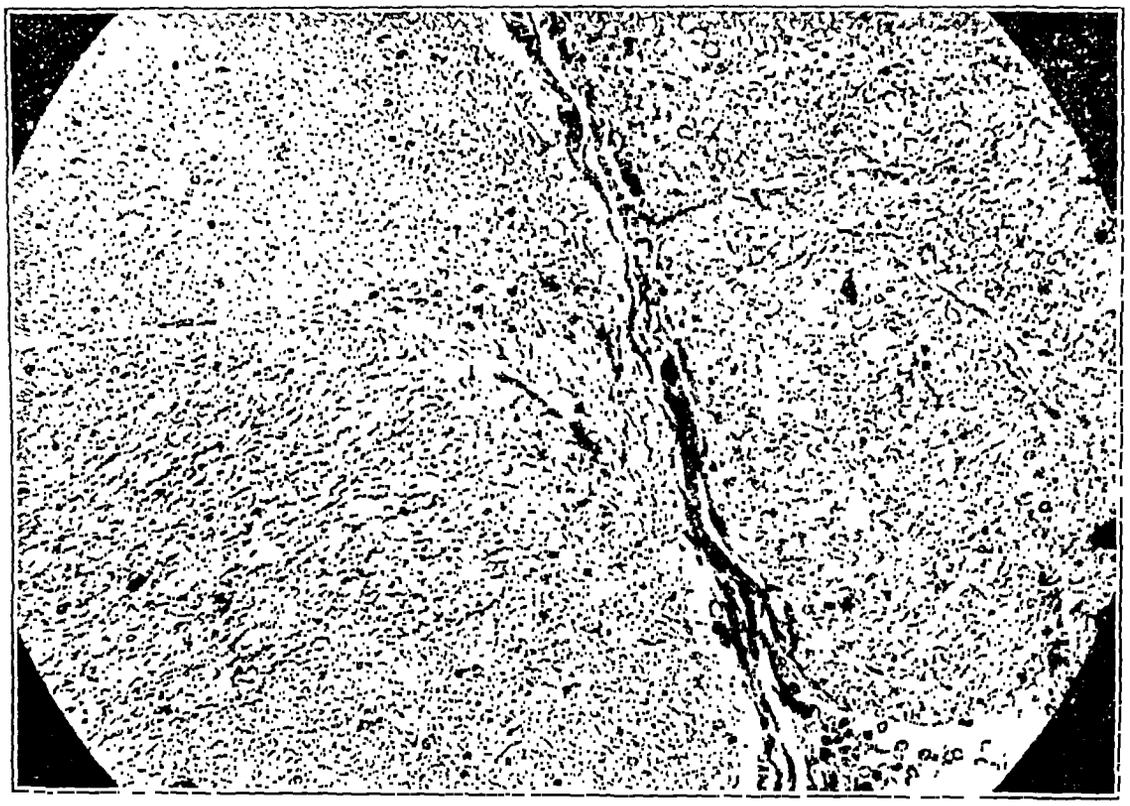


Fig 8 (case 5).—Lumbar segment of the spinal cord (left) and adjacent dorsal root (right) separated by meninges. Demyelination and vacuolation in the intramedullary and extramedullary fibers of the posterior root. Azocarmine stain; Bausch and Lomb 10 mm. lens, ocular 2.

brachial plexus was normal. Both Schwann cells and endoneurial connective tissue were increased in the posterior roots and in the proximal portions of the sciatic, femoral and obturator nerves.

CASE 5.—A. K., a 55 year old white man, a printer, was examined in University Hospital in 1932 because of lancinating pains in the feet, of two years' duration. At that time no abnormalities were found at the neurologic or the hematologic examination. The pains continued; and when he was reexamined in 1934, he presented ataxia, spasticity and paresis in the lower extremities, diminished knee jerks, absence of the achilles and plantar reflexes and absence of vibratory sensation and the sense of position in the lower extremities. No free acid was present in the gastric juice after administration of histamine; the hemoglobin of the blood was 11.2 Gm.; the red cell count was 3,410,000 and the white cell count 1,500 per cubic millimeter, and the Price-Jones curve was shifted to the right. A typical

Death was caused by the gastric neoplasm and its metastases six months after admission, thirteen years after the onset of symptoms and nine years after the institution of continuous antianemia therapy.

Pathologic examination showed a small adenocarcinoma of the greater curvature of the stomach, with extensive metastases to the liver and regional lymph nodes, obstructive icterus, cloudy swelling of the liver, edema and ascites. The bone marrow from a rib and a vertebral body was almost exhausted, the cellular content averaging 20 per cent.

Mild posterolateral sclerosis was present in the spinal cord. Marchi preparations of the femoral and sciatic nerves and of the posterior roots showed relatively mild formation of Marchi globules and mild swelling and distortion of the myelin sheaths. Azocarmine sections from the same areas showed increased connective tissue and Schwann cells, particularly in the posterior roots. No abnormalities were found in the brachial plexus.

COMMENT

Pathologic reports describing the status of the peripheral nerves in pernicious anemia are scarce and contradictory; descriptions of cases showing the influence of liver therapy have not been found in the literature. Intact peripheral nerves are described in the pathologic reports of Lichtheim,[3] Minnich,[4] Nonne,[5] Burr,[6] Boedeker and Juliusberger[7] and Homen.[8] Bramwell[9] alleged that the absence of lesions of the peripheral nerves was a characteristic feature of pernicious anemia. Von Noorden,[10] who described severe degeneration of both tibial nerves in 1 case, was apparently the first to verify by pathologic methods the presence of degeneration in the peripheral nerves, and Eisenlohr[11] shortly thereafter described degeneration of the internal saphenous nerve associated with subacute combined degeneration. Russell, Batten and Collier[12] found severe damage to the peripheral nerves in 1 case, mild degeneration of nerves in 2 cases and no abnormalities of the nerves in 3 other cases. Hamilton and Nixon[13] examined the anterior tibial nerve in 7 cases; Marchi degeneration was present in 6 and Weigert degeneration in 4 cases. Buzzard and Greenfield[14] stated that the peripheral nerves were normal in cases of pernicious anemia, but in a later report, by Greenfield and Carmichael[15] this opinion was reversed; biopsy sections from the anterior tibial nerves of 4 patients with pernicious anemia were stained with osmic acid and compared quantitatively with normal nerves and with nerves degenerated from other causes. The myelin sheaths, particularly among the nerve fibers of larger caliber, were reduced in number in the patients with pernicious anemia.

Cases 1, 2 and 3 in the present series are examples of untreated pernicious anemia of many years' duration, in severe hematologic relapse at the time of pathologic examination. In all there was evidence of degeneration of the peripheral nerves, manifested by reduction in myelin sheaths and axis-cylinders; degeneration of myelin, increase in Schwann cells and endoneurial connective tissue, axonal reaction changes in the ganglion cells of the posterior root ganglia and degenerative changes in the intramedullary course of afferent posterior root fibers. Generalized involvement of the central and peripheral nervous system is illustrated by case 2.

Cases 4 and 5 exemplify treated pernicious anemia, with the patients in hematologic remission at the time of death. The blood values for a thirteen year period were not known in case 4. The patient's bone marrow was moderately hyperplastic; but with the regular intake of liver, the stationary status of symptoms and the normal blood values at the time of his terminal illness, a severe hematologic relapse is unlikely. Moderately severe nerve degeneration was present in this case. In case 5, in which the blood values were known to have been normal for eleven years prior to the terminal illness, there were the fewest signs of degeneration of the peripheral nerve.

It has been frequently observed that the improvement in neurologic function with liver therapy is greatest when there is a scarcity or absence of pyramidal tract signs, i. e., when manifestations commonly assigned to dysfunction of the posterior column predominate. Since such disturbances as ataxia, impairment in vibratory sensation, impairment in the sense of motion and position, diminished intensity or absence of deep tendon reflexes and impaired bladder function may be caused by degeneration of extramedullary nerve pathways, which possess a powerful regenerative apparatus, it is suggested that the improvement with therapy is due to regeneration of peripheral nerves. An optimistic and

3. Lichtheim: Zur Kenntniss der perniciösen Anämie, Verhandl. d. Cong. f. inn. Med. **6**:84-99, 1887.

4. Minnich, W.: Zur Kenntniss der im Verlauf der perniciösen Anämie beobachteten Spinalerkrankungen, Ztschr. f. klin. Med. **21**:25-60 and 264-314, 1893; **22**: 60-86. 1893.

5. Nonne, M.: Weitere Beiträge zur Kenntniss der im Verlaufe letaler Anämien beobachteten Spinalerkrankungen, Deutsche Ztschr. f. Nervenh. **6**:313-368, 1894-1895.

6. Burr, C. W.: The Spinal Cord Lesions and Symptoms of Pernicious Anemia, Univ. M. Mag. **7**:472-491, 1894.

7. Boedeker and Juliusberger: Demonstration von Rückenmarksveränderungen bei tötlicher Anämie, Centralbl. f. Nervenh. **7**:315-318, 1896.

8. Homen, A.: Des lesions non-tabetiques des cordons postérieurs de la moëlle épinière, Rev. neurol. **8**:930-941, 1900.

9. Bramwell, B.: On the Association of Pernicious Anemia with Subacute Combined Degeneration of the Spinal Cord, Edinburgh M. J. **14**:260-276, 1915.

10. von Noorden, C.: Untersuchungen über schwere Anämien, Charité-Ann. **16**:217, 1891; cited by Nonne.[5]

11. Eisenlohr: Ueber primäre Atrophie der Magen- und Darmschleimhaut und deren Beziehung zu schwerer Anämie und Rückenmarkserkrankung, Deutsche med. Wchnschr. **18**:1105-1107, 1892.

12. Russell, J. S. R.; Batten, F. E., and Collier, J.: Subacute Combined Degeneration of the Spinal Cord, Brain **23**:39-110, 1900.

13. Hamilton, A. S., and Nixon, C. E.: Sensory Changes in the Subacute Combined Degeneration of Pernicious Anemia, Arch. Neurol. & Psychiat. **6**:1-31 (July) 1921.

14. Buzzard, E. F., and Greenfield, J. G.: Pathology of the Nervous System, London, Constable & Co., 1921.

15. Greenfield, J. G., and Carmichael, E. A.: The Peripheral Nerves in Cases of Subacute Combined Degeneration of the Cord, Brain **58**:483-489, 1935.

aggressive therapeutic attack is therefore justifiable, contrary to the opinion of some authors,[16] particularly when there is a disorder in those functions shared by the peripheral nerves and the posterior columns of the spinal cord.

## SUMMARY

Degeneration of the peripheral nerves was found on pathologic examination in 4 cases of pernicious anemia with posterolateral sclerosis in which autopsy was performed, and biopsy gave evidence of peripheral neuropathy in an additional case. The changes were less severe in the 2 cases in which liver therapy had been given and the patients were not in hematologic relapse at the time of pathologic examination. The great regenerative capacity of peripheral nerves offers an anatomic explanation for the clinically observed improvement with liver therapy in some of the neurologic manifestations of the disorder.

16. Grinker, R. R., and Kandel, E.: Pernicious Anemia: Results of Treatment of the Neurologic Complications, Arch. Int. Med. **54**:851-871 (Dec.) 1934.

# EMOTIONS AND ADRENERGIC AND CHOLINERGIC CHANGES IN THE BLOOD

OSKAR DIETHELM, M.D.; EDWIN J. DOTY, M.D., AND ADE T. MILHORAT, M.D.
NEW YORK

In pursuit of previously published studies,[1] the problem presented itself whether a relationship can be established between substances in the blood having adrenergic and cholinergic properties and specific emotional reactions. Investigations were carried out on patients suffering from various psychopathologic reactions in which different emotions of varying intensity were demonstrable, and on members of the staff and medical students. All subjects were without demonstrable somatic disease.

## PHARMACOLOGIC METHODS

The effect of samples of fresh whole blood on the contractions of an isolated strip of the rabbit duodenum was investigated by the following procedure: Healthy adult rabbits were killed by a blow on the head. The intestine was cut at the pylorus, and a strip approximately 10 cm. long was removed immediately and, with careful handling, was washed in Ringer-Tyrode solution. A section from 1 to 1.5 cm. long, attached to a recording lever, was suspended in about 180 cc. of the Ringer-Tyrode solution, and the contractions were recorded on a kymograph. The portion of the duodenum nearest the pylorus was found to be most suitable for the purpose. The solution was gently agitated throughout the experiment by means of a stream of air bubbles. The bottle containing the muscle strip and the Ringer-Tyrode solution was suspended in a water bath at 37 C. (fig. 1).

The blood was drawn from the patient's median cubital vein and mixed immediately with heparin in a small Erlenmeyer flask, and within a period of three minutes 5 cc. was added to the Ringer-Tyrode solution.

All observations were made on two strips of muscle simultaneously. At the conclusion of every experiment the muscle was tested by adding acetylcholine or epinephrine to the solution. The amounts of heparin used were found to be without influence on the spontaneous activity of the muscle or on the response to the pharmacologic agents used.

## PSYCHOLOGIC AND PSYCHOPATHOLOGIC CONSIDERATIONS

The emotional reactions studied included anxiety, fear, tension, resentment, anger, depression, elation and sexual excitement. In some experiments, the emotional reactions were clear-cut. In others, two or more emotions were present, frequently making differential evaluations impossible. The emotions were studied by careful observation of the person's behavior before and during the experiment, by ascertaining his subjective detailed description of emotions and sensations in conscious and in dream life and by investigation of the influence of these emotions on attention, concentration, thinking and retention. In psychologic and psychopathologic studies of emotions it has been found that, depending on the type and intensity of the emotions, the aforementioned psychologic functions were affected differently. With these methods of subjective and objective observation and investigation, an attempt was made to evaluate the type, intensity and duration of the emotions before and during the taking of the blood. Anxiety was distinguished from fear by the absence of a definite thought content, a psychologic distinction which has been supported physiologically by their different influence on the dextrose tolerance curve.[2] Tension, which other authors have considered prolonged anxiety, seems to be a special type of

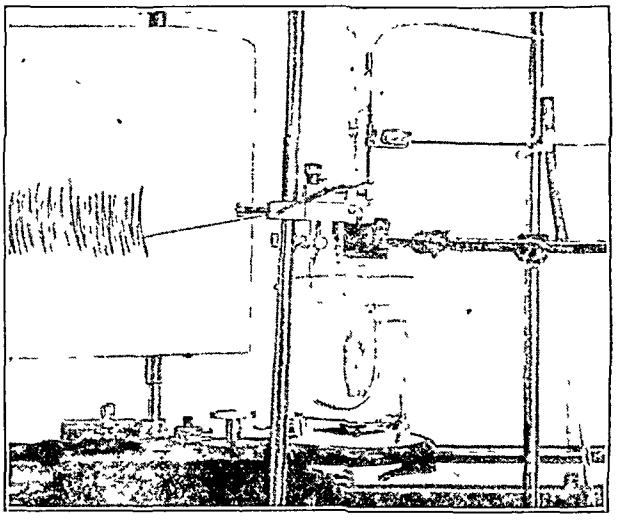


Fig. 1.—Setup of the experiment.

From the New York Hospital and the Departments of Psychiatry and Medicine, Cornell University Medical College.

1. Milhorat, A. T.; Small, S. M.; Doty, E. J., and Bartels, W. E.: Probable Mechanism by Which Somatic Changes in Certain Emotional States Are Mediated, Proc. Soc. Exper. Biol. & Med. **53**:23 (May) 1943.

2. Diethelm, O.: Influence of Emotions on Dextrose Tolerance, Arch. Neurol. & Psychiat. **36**:342 (Aug.) 1936.

emotion, arising from the struggle of contradictory strivings and of seeking difficult goals. The subject feels "taut" and notices sensations of muscular tension, especially in the muscles of the head and neck and, less frequently, of the arms, legs or trunk. Attention, concentration and retention are affected to a greater degree with tension than with anxiety. Anger occurs readily in irritable, tense states. Sometimes anger may be the climax of resentment. This emotion is recognized subjectively in feelings, and, if more intense, objectively in the expression of hostility. Depression and elation are rarely found in psychopathologic states without the accompaniment of anxiety or tension. In this study, depression and elation were observed in pure form in a slight degree, but not in psychopathologic conditions. "Sexual excitement" is a frequently used but ill defined term in psychopathologic literature. Pathologic sexual excitement implies a general stirring up of sexual strivings; i. e., repressed as well as conscious desires may become obvious to the patient. There emerge desires which to the normally functioning personality are inacceptable, as well as those which are completely acceptable. With acceptable desires there may be emotions which accompany their frustration; with inacceptable desires, emotions which are the outgrowth of ethical conflicts. It is therefore to be expected that anxiety, fear, tension and resentment may be present during a sexual excitement. Pathologic sexual excitement presents an involved and intense emotional reaction and is different from normal sexual excitement, which anticipates the possibility of satisfaction or leads to actual fulfilment of the desires.

## CORRELATED PSYCHOPATHOLOGIC AND PHARMACOLOGIC FINDINGS

As has been pointed out in a previous publication,[1] two well defined alterations in the rhythmic contractions of the rabbit intestine were observed—a brief depression and reduction of the amplitude (similar to the influence of epinephrine) and a prolonged elevation of the base line (resembling the changes produced by cholinergic drugs). In the presence of both factors, a contracted and elevated type of curve may occur. If one of these two factors dominates, the expression of the other factor may appear less distinct than that which would correspond to the true intensity.

The curves to be presented in this paper were selected from a large number of observations on psychiatric patients and well persons to demonstrate the influence of various emotions. It should be kept in mind that distinct emotions are infrequently encountered. A careful study of one dominant emotion usually reveals the presence of less obvious, or minor, emotions. In states of ease, when no disturbing emotions, such as anxiety and tension, were present, no change occurred in the curve when the person's blood was added. (See figure 2, tests 156 and 146-2.)

1. *Anxiety.*—The adrenergic effect was of varying degree, depending on the intensity of the anxiety; the effect in the test was usually brief.

CASE 1.—A 22 year old nurse had consulted a psychiatrist several times because of anxiety reactions and difficulties in concentration caused by her work. The blood was taken at the end of a lengthy therapeutic interview in which considerable anxiety had been stirred up. She appeared anxious, clasping her hands tightly, felt "somewhat anxious" and had anxious "anticipation of the test." The test was performed a few hours before menstruation. (See figure 2, test 131.)

2. *Tension.*—The cholinergic effect was of varying degree, dependent on the intensity of the tension and its duration; the effect in the test was lasting.

CASE 2.—A 40 year old woman had suffered from tension, with difficulty in concentration and depressive moods, for several months.

March 31, 1944: The face was drawn; the body was held stiffly, and she appeared tense. She was irritable and restless and felt "jittery" and tired. There were demonstrable difficulties in passive attention and concentration and mild difficulty in retention. She was disturbed by inacceptable sexual desires. The blood was taken on the fourth day of menstruation. (See figure 2, test 129.)

April 21: The patient looked mildly tense but stated that she felt at ease; she was friendly and cheerful. No thinking difficulties were noticed. She was not menstruating at the time of the test. (See figure 2, test 138.)

April 28-June 9: Three other tests, made over a period of two months, at times of severe, as well as of mild, tension, gave the same results as those just presented. Considering her inability to resign herself fully to a personal problem, mild tension was expected to be present, even when not noticeable. The patient was unwilling to admit the presence of emotions to herself except when they were intense. During these tests the patient was not menstruating.

3. *Tension, Anxiety and Resentment.*—The adrenergic effect of resentment was of varying degree, depending on the intensity of the anxiety; the effect in the test was usually brief.

CASE 3.—A 39 year old man (not a patient) had been for two weeks under considerable strain, feeling increasingly "tense," in trying to find a solution to a difficult personal problem. When questioned more closely on Sept. 15, 1943, he mentioned a marked feeling of anxiety lest he might not find an acceptable solution and expressed resentment toward the person involved. No thinking disorder was noticed (psycho-

logic testing was omitted). The test revealed very marked adrenergic (anxiety and resentment) and somewhat less marked cholinergic (tension) factors. (See figure 2, test 61.)

anxiety lest the test would reveal that he had not been able to adjust to the situation. (He is a perfectionistic, self-reliant person, who reacts readily with anxiety to possible failures.) (See figure 2, test 64.)

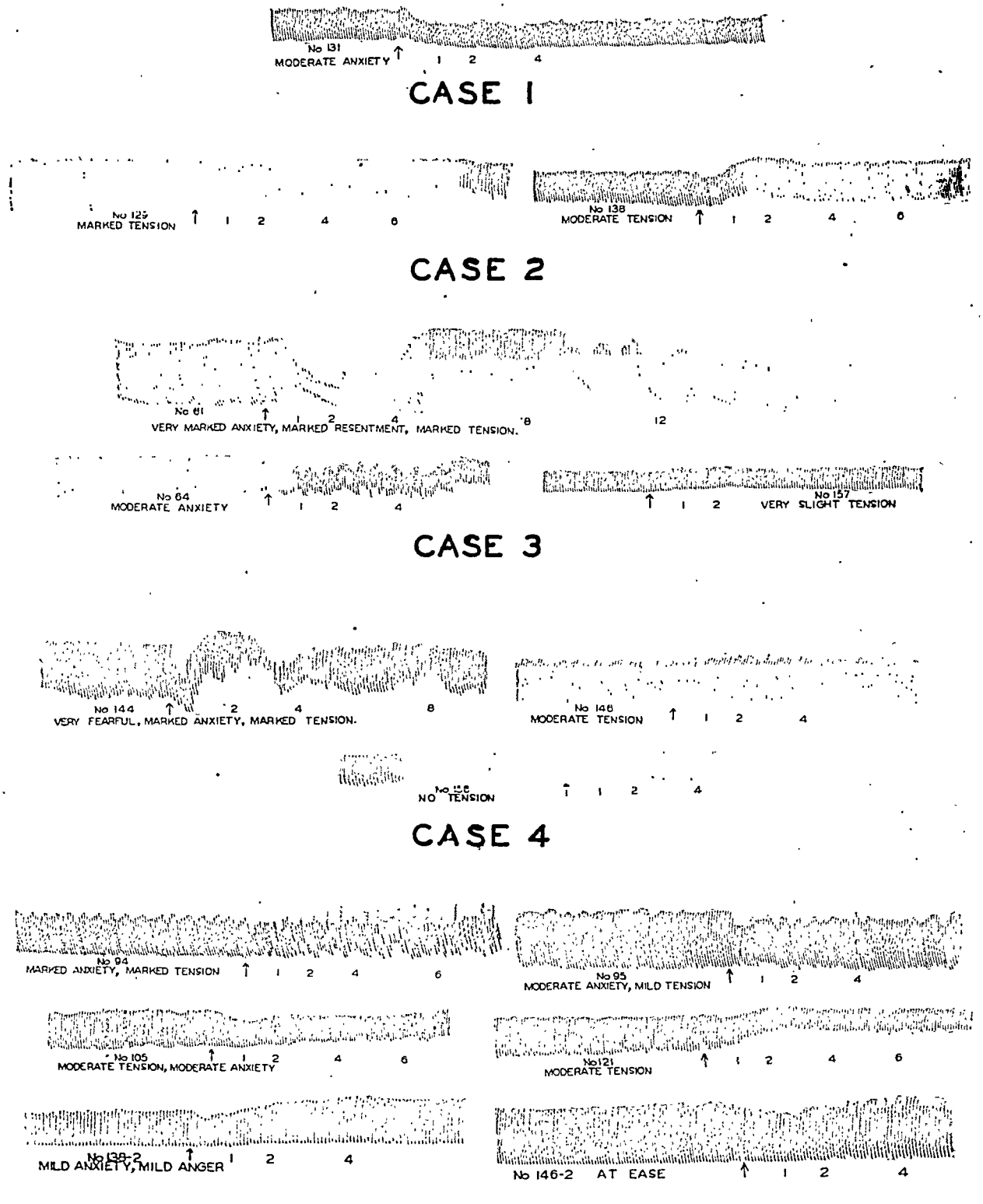



Fig. 2.—Effect on contraction of rabbit duodenum of blood of patients (cases 1 to 5) taken during various emotional states.

The sample of blood was added to the Ringer-Tyrode solution at the time shown by the arrow. The numerals indicate the time in minutes after the addition of the sample of blood.

September 17: An acceptable solution of his problem had been found on the afternoon of September 15. At the time of the test he felt relaxed but experienced

June 16, 1944: Pressure of work had led to his feeling "nervous" and "slightly irritable." His subjective statement was corroborated by the observation of a co-

worker. He appeared slightly tense. (See figure 2, test 157.)

*Additional Tests:* Four tests, made over a period of nine months, corroborated the previous findings of anxiety being accompanied with adrenergic and tension with cholinergic effects. Resentment was present only in the first test.

4. *Tension, Anxiety and Panic.*—The following case is illustrative.

CASE 4.—In this 46 year old woman there developed a depression with paranoid misinterpretations in January 1944. In April fear became the dominant emotion, accompanied with marked thinking difficulties.

May 3, 1944: With drawn face and rigid posture, the patient looked fearful, saying little. She felt "tired," "tense" and "depressed" and noticed "tightness" in her throat and palpitation. Her hands were moist. She had fearful dreams for several nights. There were subjective observations and objective signs of marked difficulty in concentration. She was not menstruating. (See figure 2, test 144.)

The marked fear (panic) and anxiety state subsided within three days. The patient remained depressed during the six week period of this investigation, but varying degrees of anxiety and tension persisted.

May 10: The patient appeared cheerful and friendly but tense. She felt "restless" and showed definite thinking difficulty (poor passive attention and difficulty in prolonged concentration). She was not menstruating. (See figure 2, test 146.)

June 14: The patient was pleasant; no signs of anxiety or tension were present. (See figure 2, test 156.)

5. *Fear, Anxiety, Tension and Sexual Pressure.*—The following case is illustrative.

CASE 5.—A 47 year old man had suffered from phobias for one and a half years. In the last two months pronounced fear and anxiety were present.

Jan. 14, 1944: The patient looked anxious, apprehensive and tense, complaining of fatigue and painful tension in the arms and legs and describing "intense anxiety" and "discouragement" and the fear that he might harm himself or others. There were mild thinking disorders, such as difficulty in concentration and slowness in remembering. (See figure 2, test 94.)

January 17: The patient felt more self confident and was greatly reassured by hospital protection. Occasionally his fears returned; he then noticed "anxiety," and often "tension" of the abdominal muscles. (See figure 2, test 95.)

February 11: The patient's psychotherapeutic progress had been excellent, but in the days preceding the test he was more tense (feeling of tightness in the back of the neck), and on the day of the test he experienced anxiety in connection with the psychotherapeutic discussion. (See figure 2, test 105.)

March 17: The patient was cheerful but complained of "uneasy sensations" in his stomach and sensations of tension in the abdominal muscles. He appeared tense. This tension was related to inacceptable sexual pressure, which he wished to control. (See figure 2, test 121.)

April 21: The patient was cheerful and pleasant. In the last few days he had expressed guilt over sexual desires. Before the test he became mildly angry over a nurse's behavior. (See figure 2, test 138-2.)

May 10: He was pleasant and denied being anxious or tense. (The patient recovered and left the hospital.) (See figure 2, test 146-2.)

6. *Sexual Excitement.*—In the blood of persons who were sexually excited, but not to a pathologic degree and without anxiety-producing factors, the adrenergic and cholinergic substances were absent in the test.

CASE 6.—This patient, a 26 year old woman, presented pathologic sexual excitement with various strong emotions. Within seventy-two hours after her first delivery, there developed marked excitement, characterized by elation, flight of ideas and intense sexual desires (overt masturbation, heterosexual aggression and, at times, fear of homosexual assault). Her emotions varied in type and intensity, outstanding among them being elation, fear, anxiety, anger and resentment.

Sept. 14, 1943: Intense sexual excitement, with fear and suspiciousness, was present. The patient was resentful toward the nurses. There was no elation. The thinking disorder was expressed in vagueness and irrelevancy. She was not menstruating. (See figure 3, test 59.)

September 17: The patient showed marked excitement, being noisy, resistive and assaultive. She was occasionally fearful, suspicious, mildly resentful and irritable. She appeared distressed and tense, her mood changing readily to elation with flight of ideas. She was erotic toward men and women, exposing herself and making sexual advances. She was not menstruating. (See figure 3, test 65.)

November 30: The patient was mildly elated and slightly irritable (mild tension) and felt somewhat insecure (mild anxiety). She was not menstruating. (See figure 3, test 82.)

7. *Anger, Anxiety and Tension.*—The adrenergic effect of anger was of varying degree, depending on the intensity of the emotion; the effect in the test was usually brief.

CASE 7.—A 30 year old woman (not a patient), reserved and conscientious, reacted readily with mild anxiety to situations in which she felt exposed.

Feb. 23, 1944: For two weeks she had been under considerable tension, being unable to solve a personal problem. For the last hour before the test there was anxiety as to what the test might reveal. The test was made on the third day of menstruation. (See figure 3, test 112.)

March 15: The subject was cheerful and at ease. She was not menstruating. (See figure 3, test 119-1.)

June 2: Resentment had been present for twenty-four hours, with anger one-half hour before the test. She was not menstruating. (See figure 3, test 152.)

8. *Pathologic Elation.*—In the patients studied, pathologic elation always presented an involved emotional reaction because other emotions, of varying intensity, were present (especially tension, resentment and anger, but also fear and anxiety).

CASE 8.—A 57 year old woman was mildly elated, demonstrating overactivity and overtalkativeness (hypomanic reaction). She appeared insecure and at times seemed to hide anxiety.

Jan. 24, 1944: The patient was elated ("felt fine"); she was pleasant but at times expressed resentment toward being considered sick. She was not menstruating. (See figure 3, test 97.)

CASE 9.—A 50 year old woman was elated ("felt fine"), overactive and overtalkative, with flight of ideas; she showed marked distractibility and was pleasant but easily angered. She had recovered from three previous manic excitements, which were followed by depressions.

May 31, 1944: The patient was pleasant and overactive and talked incessantly during the test, with marked distractibility and flight of ideas. She said she felt "fine" but was "tense." She was easily angered by the nurses, but there was no indication of resentment. She was not menstruating. (See figure 3, test 150.)

June 2: She was pleasant and overactive and talke incessantly, but with less distractibility and no flig of ideas. She said she felt "fine" and denied feelin tense. She was not angered by the nurses. She was not menstruating. (See figure 3, test 151.)

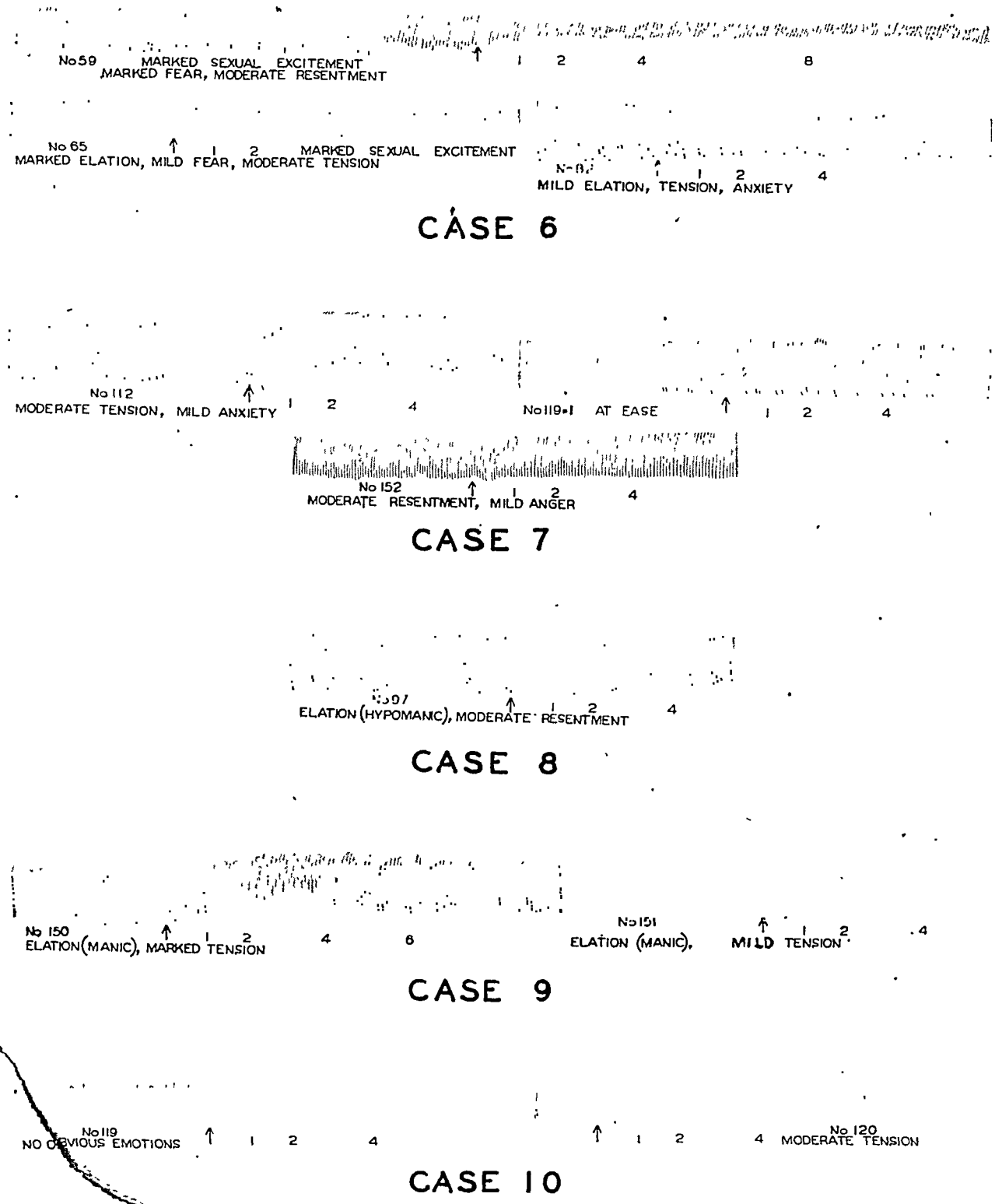



Fig. 3.—Effect on contraction of rabbit duodenum of blood of patients (cases 6 to 10) taken during various emotional states. The records were obtained with the same method as the records shown in figure 2.

9. *Freeing of Affect Under Influence of Sodium Amytal.*—In many psychopathologic conditions

emotions may not seem to play a role. Under the influence of sodium amytal these emotional reactions can become active. This experimental observation is not essentially different from the freeing of affect which occurs under successful psychotherapy. This freeing of emotions and the resulting influence on substances in the blood were observed in 3 patients.

CASE 10.—A 30 year old man had been deeply depressed for several months. He was usually pleasant. He looked sad but denied having any definite emotional reactions. When asked about specific life situations which were known to have been disturbing, he reacted with little emotion.

March 15, 1944: The patient was seen by his physician at 10:30 a. m. He discussed without emotional display an automobile accident and his suicidal attempt a few months previously. Blood was taken at 10:44 a. m. (figure 3, test 119). At 11:15 a. m. he received sodium amytal intravenously. The discussion of the same topics was resumed at 11:30 a. m. The patient remained pleasant but appeared tense and slightly irritable, and to both situations he expressed a slight feeling of guilt but with lack of corresponding emotional display. Blood was taken at 12:16 p. m. (figure 3, test 120).

## CONCLUSIONS AND SUMMARY

The experiments presented here demonstrate that during some specific emotions the blood contains factors that can produce effects on the isolated duodenum of the rabbit similar to those of epinephrine and acetylcholine. The physical condition of all the persons studied was good. Menstruation did not seem to influence the reactions.

The results of such experiments are frequently difficult to analyze because one may not be dealing with merely the one emotion which dominates the psychologic and psychopathologic picture. Emotions which are not obvious may have to be considered. Anxiety, resentment and anger are accompanied with definite adrenergic factors; tension, and possibly fear, with cholinergic factors. The blood of one patient in a depressed state with no other emotions detectable had an entirely negative effect during one observation. In other studies of depressed states and in all observations on elated states, anxiety, tension or fear was present, with corresponding adrenergic and cholinergic effects. There does not seem to be an essential difference between normal and psychopathologic emotions except in the intensity of the adrenergic and cholinergic response. The intensity of the response depends on the intensity of the emotion, and probably on individual physiologic capacity to respond.

New York Hospital.

# EFFECTS OF TRANSIENT STRETCHING OF PERIPHERAL NERVE

D. DENNY-BROWN, M.B., AND MARGARET M. DOHERTY, A.B.
BOSTON

Reports of nerve injuries resulting from war wounds frequently include evidence of damage to peripheral nerves without loss of anatomic continuity. A spindle-shaped neuroma is frequently reported in such circumstances.[1] In other cases a lasting loss of excitability of the nerve is traced to a region of intraneural thickening or fibrosis. Similar findings are encountered in cases of traction injury to the brachial plexus in civilian practice.[2] The condition is usually attributed to intraneural hemorrhage immediately following injury and its replacement by fibrosis.[2] Such cicatrices have usually a very poor prognosis for recovery of function, though occasionally remarkable recovery may occur spontaneously. In attempting to ascertain the features which enable good recovery to be made through some "spindle neuromas" and the factors which prevent recovery in others, we have studied the effect of percussion of nerve experimentally.[3] Percussion will produce with regularity a pseudoneuroma, or localized bulge on the nerve associated with either transient partial paralysis or complete paralysis and peripheral degeneration, according to the intensity of the process. In the most severe degree, however, regeneration was rapid and complete and residual fibrosis minimal in amount. The only hint of more severe complication was the occasional rupture of the perineurial sheath, which was accompanied with some herniation of the nerve bundles, with consequent loss of nerve fibers at this point. We were unable to induce by this means the dense intraneural fibrosis commonly encountered by the neurosurgeon. On the other hand, we also found that with gentle kneading of a nerve trunk a severe intraneural hemorrhage could be induced, and that within limits this could be rapidly resolved, with return of function within a few days or after due regeneration. Intraneural hemorrhage could not therefore per se lead to fibrosis. We then turned to study the different mechanism of stretching injury to nerve, in search of the event leading to fibrosis.

In view of the great distortion of soft tissues produced by the passage of a projectile through them, the possibility of sudden longitudinal stretch appears likely. The experiments of Black and associates,[4] in which blocks of gelatin and the muscles of an animal limb were shown to undergo wide expansion and contraction for many milliseconds after passage of the projectile, indicated the presence of powerful and extremely rapid tensions far beyond the limits of the small ultimate track of the projectile. Such rapidity of tension is difficult to reproduce experimentally without other damage, and the present report is concerned with the effects of a steady pull for some five to ten seconds exerted by the firm grasp of the gloved fingers of the operator.

Previous reports on the histologic and functional disorder resulting from stretch are scanty. Late in the last century nerve stretching was widely used in the treatment of neuralgias of various types, chiefly owing to some physiologic evidence (Sheving, and Debove and Laborde, cited by Takimoto[5]) that stretching of normal nerves injured sensory conduction before motor conduction. It is probable that the differential effect was the result of damage to nerve roots or to the spinal cord. Vogt,[6] Stintzing[7] and Fenger and Lee[8] reviewed the indications for

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

1. Tinel, J.: Nerve Wounds, translated by F. Rothwell and C. A. Joll, London, Baillière, Tindall & Cox, 1917. Seddon, H. J.: Three Types of Nerve Injury, Brain **66**:237, 1943.

2. Stookey, B.: Surgical and Mechanical Treatment of Peripheral Nerves, Philadelphia, W. B. Saunders Company, 1922.

3. Denny-Brown, D., and Brenner, C.: The Effect of Percussion on Nerve, J. Neurol., Neurosurg. & Psychiat. **7**:76, 1944.

4. Black, A. N.; Burns, B. D., and Zuckerman, S.: An Experimental Study of the Wounding Mechanism of High-Velocity Missiles, Brit. M. J. **2**:872, 1941.

5. Takimoto, B.: Ueber die Nervendehnung: Experimentelle und klinische Untersuchung, Mitt. d. med. Fak., Tokyo **16**:73, 1916.

6. Vogt, P.: Die Nerven-Dehnung als Operation in der chirurgischen Praxis, Leipzig, F. C. W. Vogel, 1877.

7. Stintzing, R.: Ueber Nervendehnung: Eine experimentelle und klinische Studie, Leipzig, F. C. W. Vogel, 1883.

8. Fenger, C., and Lee, E. W.: Nerve Stretching, J. Nerv. & Ment. Dis. **8**:263, 1881.

the procedure and the methods employed. Vogt [6] also cited animal experiments and described the extravasations of blood in the epineurium induced by stretching. He noted the tortuous vessels and anastomoses which remained. Witkowski,[9] in 1881, described changes in the myelin sheath of nerve fibers, consisting of a widening of the incisures of Schmidt and Lantermann immediately after stretching and degeneration, more marked in the periphery of the nerve bundles, if an interval of survival was allowed (rabbit, guinea pig). Traction was exerted by pulling the nerve with a hook. Weir Mitchell [10] observed that the sciatic nerve of a rabbit could be stretched "until the lengthening was equal to three-fourths of an inch in three inches" before motor conduction failed.

Takimoto [5] reviewed the whole subject of nerve stretching as a surgical treatment and cited both animal experiments and human cases. He noted the enormous weight (approximately 32 Kg.) necessary to stretch the human sciatic nerve. Tillaux [11] had earlier observed that a weight of 54 to 58 Kg. was necessary to rupture the nerve. Takimoto used weights of 100 to 400 Gm. attached to a sling to stretch the sciatic nerve of rabbits. Hemorrhages in the nerve were not a necessary part of the lesion and were sometimes absent with extensions as great as 750 Gm. When hemorrhages occurred, they were usually in the epineurium. Few occurred within the perineurium. The striking immediate change was either the breaking up of axis-cylinders into short segments or thinning at regular intervals so as to produce beading. The Schmidt-Lantermann incisures on the myelin sheaths widened, and rupture occurred at these points. If survival was allowed for periods of six to forty-eight hours, the nerve became edematous, and droplets of myelin were found near the nodes of Ranvier. Degeneration of myelin sheaths began after three days and was more severe in the periphery of the nerve bundle. If the stretch was not severe, motor function was less affected than sensory, and a return of motor function could be observed in as brief an interval as twelve minutes. In the clinical cases cited there was no relief of referred pain, and the procedure was not recommended for the abolition of this type of pain. Sections from human nerves confirmed the beading of axis-cylinders in the region of nerve stretched.

The widening of the incisures of Schmidt and Lantermann produced by stretching was noted also by Glees,[12] who examined the phenomenon in fresh fibers under polarized light. He concluded that these structures are a mechanism permitting extension of nerve fibers.

9. Witkowski, L.: Zur Nervendehnung, Arch. f. Psychiat. **11**:532, 1881.

10. Mitchell, S. W.: Injuries of Nerves and Their Consequences, Philadelphia, J. B. Lippincott & Co., 1872.

11. Tillaux, P.: Des affections chirurgicales des nerfs, Thesis, Paris, P. Asselin, 1866.

## METHOD

The very rapid longitudinal stretch of nerve that must occur in injuries produced by projectiles and also in the more usual violence of civilian accidents is extremely difficult to reproduce experimentally in uncomplicated form. Traction on a nerve with a hook, as used by earlier investigators, has the disadvantage that the situation of first injury is unknown, and may often be the nerve roots. We have therefore used the procedure of grasping the nerve as gently as possible between the fingers of two hands and stretching a known segment. The tension applied was not measured, but in all later experiments the lengthening of the nerve was gaged by first applying loose ligatures at measured intervals and then measuring the intervals after stretch. This method is only approximate, for sometimes the nerve would give under the fingers and not at the place expected. The procedure was carried out on cats at open operation, with the animal under deep pentobarbital anesthesia. After the first few experiments the nerve used was the peroneal.

## OBSERVATIONS

*Effect of Stretch on Sciatic Nerve.*—The sciatic nerve of the cat, exposed at operation with the animal under pentobarbital anesthesia, proved to be difficult to stretch without injury to the nerve at the points at which force is applied. The most satisfactory method was found to be by hooking the nerve between gloved fingers of each hand and pulling in opposite directions. The tension required to elongate the nerve in any appreciable degree was considerable, and it was inevitable that some of the tension was directed to the central and peripheral attachments of the nerve. Our attempts to stretch this nerve were abandoned after 2 experiments, in which petechial hemorrhages appeared over a length of 2 cm. in one and of 4 cm. in another, after a maximum effort had been made to elongate the main trunk of the nerve. In neither instance was any weakness of plantar flexion or dorsiflexion of the foot or of spreading of the toes observed twenty-four hours after the operation. Appreciation of touch and pinch to the foot appeared to be intact.

The animal was allowed to survive for nine days in each experiment. In the nerve which

12. Glees, P.: Observations on the Structure of the Connective Tissue Sheaths of Cutaneous Nerves, J. Anat. **77**:153, 1943.

initially had shown epineurial hemorrhage over a length of 2 cm., the epineurial vessels were all tortuous, and one small arteriole was found to be thrombosed. The epineurial fibroblasts were more prominent than usual and appeared to have been activated by the trauma. The nerve bundles showed no degeneration, but several changes were observed in the Schmidt-Lantermann incisures.

On the side on which more extensive initial epineurial hemorrhage had been present, a number of ruptured vessels were found, one small fasciculus was degenerated and patchy edema was found in another, with swelling of axis-

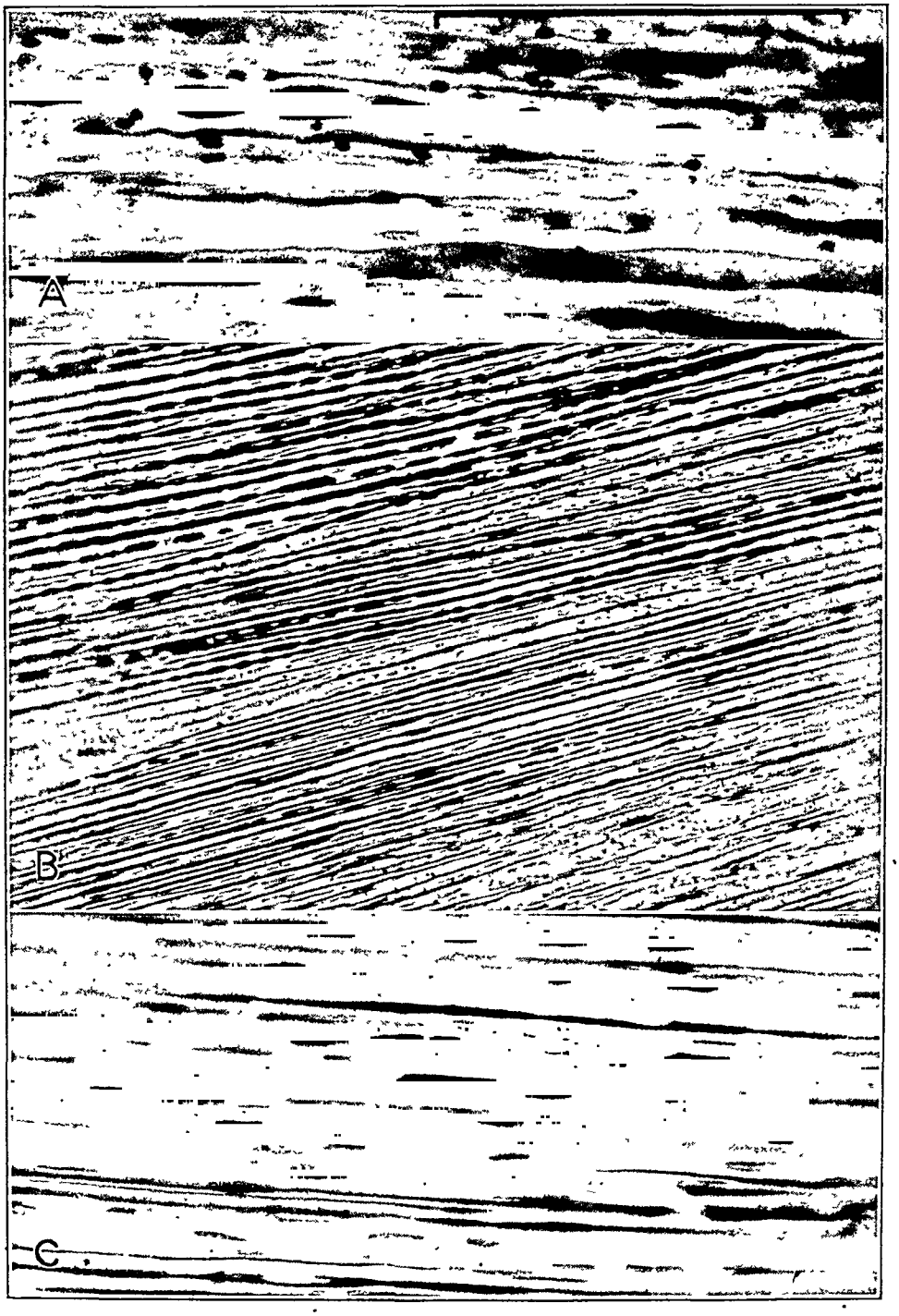



Fig. 1.—*A*, greatly swollen, but otherwise intact, axis-cylinders in an edematous segment of sciatic nerve nine days after stretching. The ruled line in the upper right corner corresponds to 0.1 mm. Gros-Bielschowsky method. *B* (experiment 3, table), beading and swelling of axis-cylinders in peroneal nerve twenty-eight days after stretching, with partial recovery of motor function. *C*, higher magnification of beading of axis-cylinders.

bundles were edematous over an extent of 5 to 10 mm. and in this area showed remarkable swelling of the axis-cylinders (fig. 1 *A*). The myelin was swollen and slightly irregular. No cylinders. With the edema on both sides was some proliferation of endoneurial cells, with a few mononuclear histiocytes. There was no beading of axis-cylinders or myelin.

These changes are consistent with patchy partial ischemia of the nerve and were identical with those found by us[13] after ligature of the vessels of the sciatic nerve, with which the free longitudinal vascular anastomosis allows only minimal edematous reaction. It would appear that the effort to stretch the nerve had resulted in rupture of a small epineurial vessel, with minimal consequences.

We therefore turned to more slender nerves.

*Effect of Stretch on the Peroneal Nerve.*—By section of the biceps femoris muscle of the cat near its insertion and reflection of the lower portion of the muscle posteriorly, the peroneal nerve, from its origin from the sciatic nerve to its disappearance into the pretibial muscles, can be exposed. Ligature and section of some vessels passing between the popliteal space and the biceps muscle are necessary to expose it completely throughout its course. The nerve can be freed throughout its length without damage to its blood supply, which enters at the ends. Loose ligatures were applied to the nerve, and the distance between them was measured before and after stretch.

When stretch is applied with the gloved fingers, the peroneal nerve is felt to extend moderately easily, in the manner of a plastic material, so that with little force its length can be doubled. On release it remains near the new length and lies in redundant folds. The increase in length occurs about the middle of its course, and more commonly in its proximal than in its distal half.

Altogether, 10 experiments of this type were carried out, with varying degrees of stretch and varying durations of survival, from five to one hundred and forty days. Three other experiments were made on small cutaneous nerves, such as the sural. The immediate consequences of a single stretch applied in this manner were simple lengthening, epineurial hemorrhage or partial rupture of the sheath. On no occasion was stretching carried to the point of complete rupture. These consequences will be dealt with separately.

*Data on Ten Experiments Showing Effects of Transient Stretch of Peripheral Nerve*

| Experiment No. | Original Interval, Mm. | Interval After Stretch, Mm. | Immediate Pathologic Change | State After 24 Hours | Onset of Recovery, Days | Duration of Complete Recovery, Days | Duration of Experiment, Days | Motor Conduction at End of Experiment | Histologic Changes |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 31 | 49 | Nil | Severe weakness | 1 | 12 | 13 | Full | Patchy edema, beading, microscopic hemorrhage |
| 2 | 6 | 13 | Nil | Paralysis | 3 | 28 | 28 | Full | Patchy edema, beading, regeneration |
| 3 | 6 | 25 | Nil | Paralysis | 3 | Incomplete | 28 | Fair | Patchy edema, beading, small areas of regeneration |
| 4 | 10 | 20 | Nil | Paralysis | 12 | 31 | 75 | Full | Edema, regeneration, some occluded epineurial arterioles |
| 5 | 10 | ? 20 | Nil | Weakness | 1 | 14 | 140 | Full | Beading in periphery of some fasciculi |
| 6 | 12 | 33 | Small epineurial hemorrhage | Paralysis | 41 | 64 | 75 | Full | Edema of all fasciculi; some occluded small epineurial vessels; regeneration |
| 7 | 30 | 43 | Small hernia | Paralysis | .. | .. | 5 | Nil | Small rupture of perineurium; thin limiting membrane remaining; congestion of endoneurial vessels |
| 8 | 31 | 46 | 4 mm. hernia | Paralysis | .. | .. | 5 | Nil | Swelling showed rupture of perineurium; thrombosed epineurial vessels; loss of axons and myelin in and above swelling |
| 9 | 30 | 54 | Large hernia | Paralysis | .. | .. | 13 | Nil | Large fibroblastic mass infiltrating muscle, proximal and distal necrosis of nerve |
| 10 | 10 | ? 20 | Small hernia | Paralysis | 21 | 48 | 140 | Full | Pseudoneuroma with almost perfect regeneration |

It was at first remarkable that the peroneal nerve could be stretched until the distance between markers on it increased 100 per cent, often without any sign of hemorrhage, and with only slight weakness twenty-four hours later, when the animal had recovered from anesthesia. Recovery of apparently full power of dorsiflexion of the foot and spreading of the toes occurred within fourteen days. We did not attempt to define the sensory disturbance.

In experiments 1 and 5 (table) restoration of both function and structure appeared to be complete after the interval indicated, except that the larger axis-cylinders appeared swollen and had a segmented appearance in some of the nerve bundles (fig. 1 *B* and *C*). Such segmentation was usually more prominent at the periphery of the nerve bundle. The myelin appeared to

13. Denny-Brown, D., and Brenner, C.: Paralysis of Nerve Induced by Direct Pressure and by Tourniquet, Arch. Neurol. & Psychiat. **51**:1 (Jan.) 1944.

be of normal structure, though it was occasionally beaded. Each node was noted to be heavily stained.

A stretch of over 100 per cent (experiments 2, 3, 4 and 6) induced occasionally immediate small, petechial epineurial hemorrhages. The nerve appeared pale and thin. Complete paralysis was present after twenty-four hours. Recovery of function occurred progressively and was complete in about one month except when epineurial hemorrhage had occurred. In this case regeneration was also found to be complete but more obvious histologic changes remained. The nerve bundles were often edematous, with widely distended perineurial spaces, as in figure 2 *D* and *E*. The neural fibroblasts had proliferated so that the endoneurium was more cellular and stained slightly more intensely for collagen

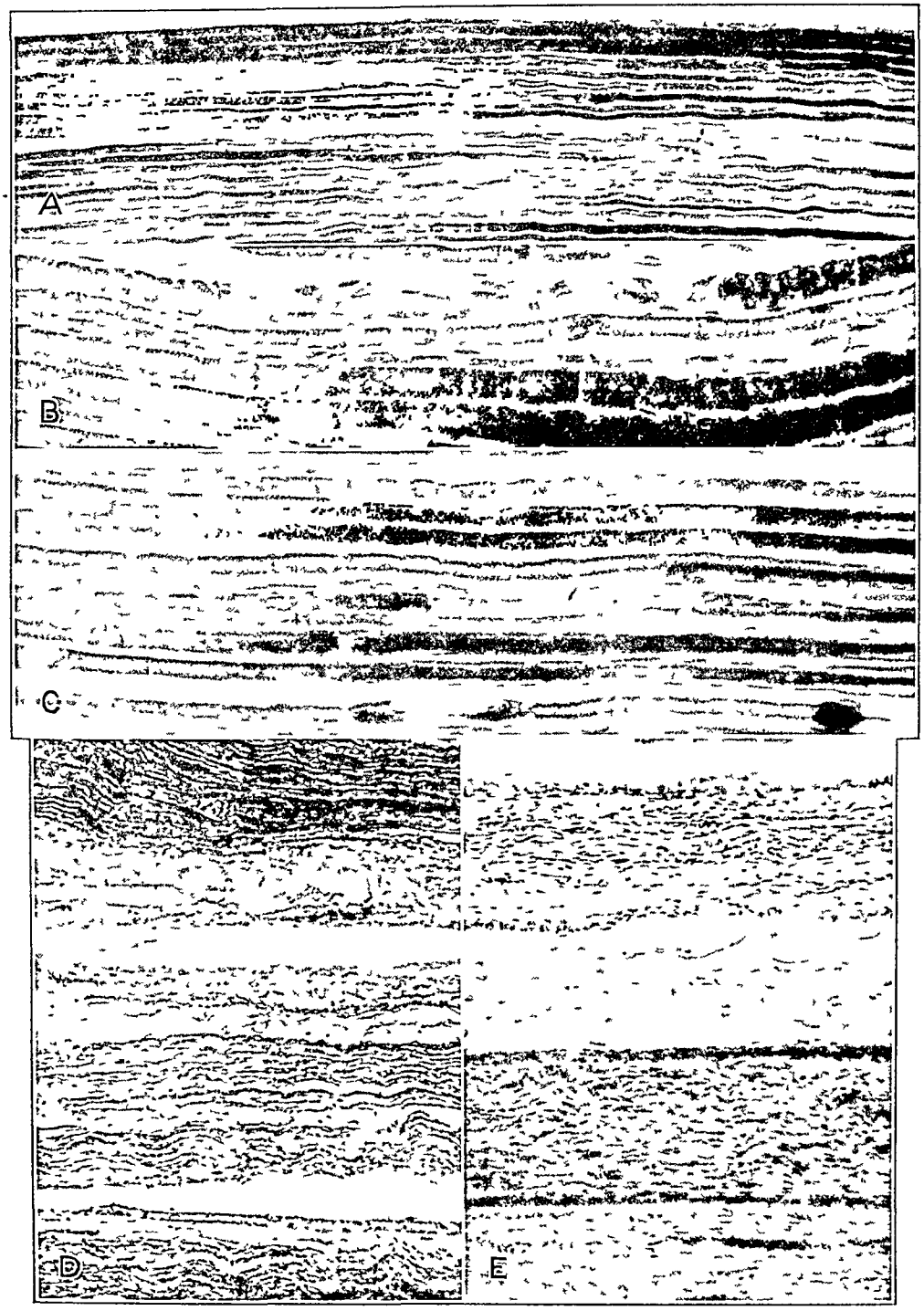



Fig. 2.—*A*, peroneal nerve one hundred and forty days after stretch, showing the numerous regenerated, thin myelin sheaths; Spielmeyer stain for myelin. *B*, same nerve as that presented in *A*, showing gap in myelin sheath in an undegenerated fiber; sudan III and hematoxylin stains. *C*, fiber similar to that presented in *B*, showing other types of gaps in the myelin sheath and beading of myelin; Spielmeyer stain for myelin. *D*, peroneal nerve (experiment 1, table), showing edema of the neural fasciculus in the center, as compared with an unaffected fasciculus above; Gros-Bielschowsky stain. *E*, peroneal nerve (experiment 4), showing edema of a fasciculus seventy-five days after stretching; hematoxylin and eosin stain.

than the unaffected bundles. Many of the nerve fibers had the thin myelin of regeneration (fig. 2*A*). The original areas of damage to nerve fibers were seen as patchy distention of the

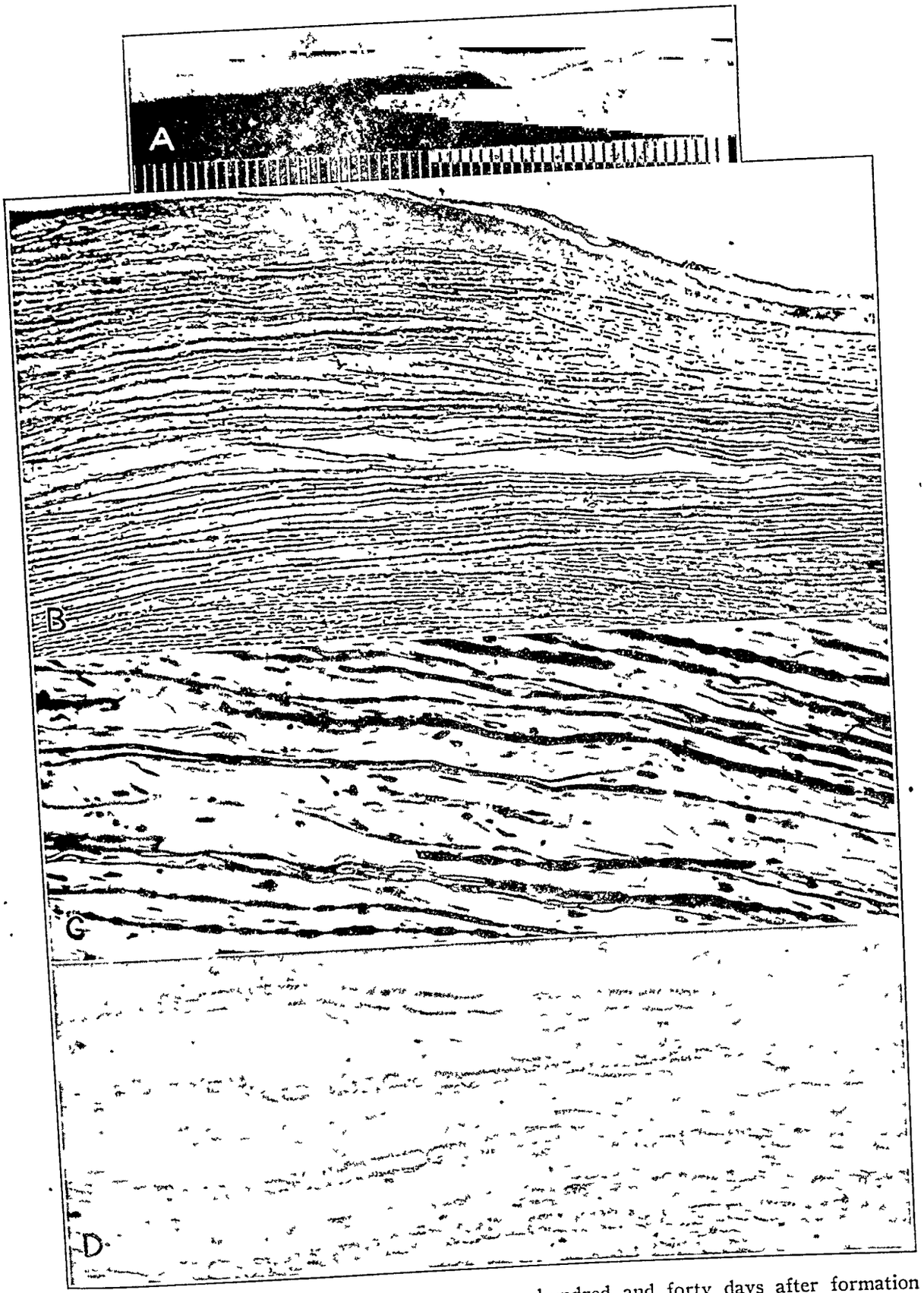



Fig. 3.—*A*, "pseudoneuroma" in the peroneal nerve one hundred and forty days after formation of a small hernia. The proximal end of the nerve lies to the left. The scale is in millimeters. *B*, distal side of the pseudoneuroma shown in *A*. Gros-Bielschowsky–cresyl violet method. *C*, section of field shown in *B*, with higher magnification *D*, from same field as that shown in *C*, with phosphotungstic and hematoxylin stain (Mallory).

edema. The more severe and prolonged the initial paralysis, the more extensive was the subsequent edematous change. In experiment 6 (table) all the fasciculi of the nerve were then involved throughout their extent. The perineurium over such bundles was slightly thickened

nerve bundle with fluid, with moderate increase in neural fibroblasts, and interpreted as neural

in places but was otherwise intact. The epineurium showed increase of young fibroblasts in some areas and a notable dilatation of all the veins. Some of the arterioles had greatly thickened walls and proliferation of the intima, and here and there a small artery was thrombosed.

was also found, but this was not prominent. The degeneration was directly related to vascular damage in the epineurium. That it was essentially ischemic in nature was shown by the frequent finding of large gaps in the myelin sheath of otherwise intact fibers on or near the degenera

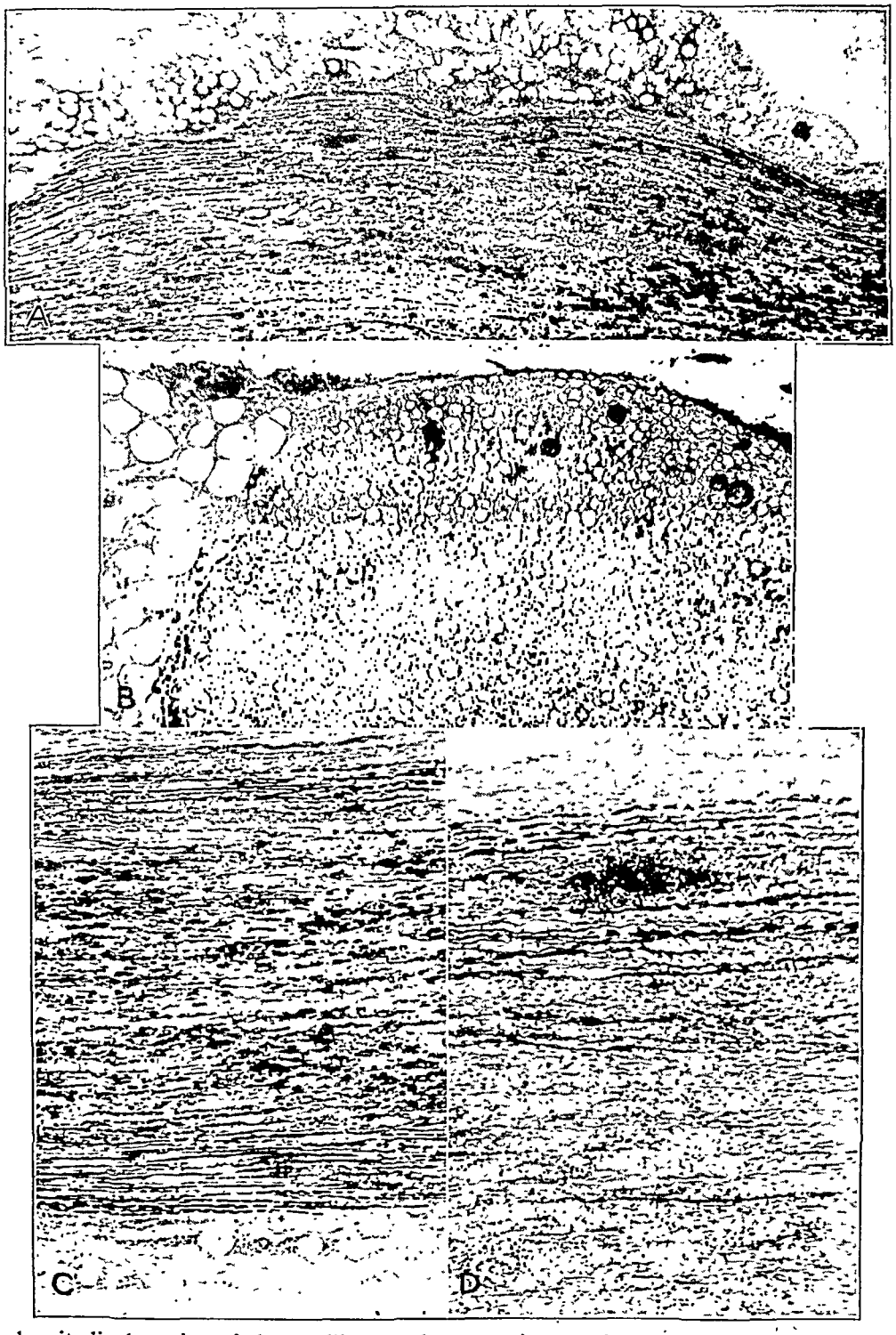



Fig. 4.—*A*, longitudinal section of the swelling on the nerve in experiment 8 (table), showing loss of structure in center five days after stretch; Gros-Bielschowsky–cresyl violet stain. *B*, transverse section of small swelling five days after stretch (experiment 7); phosphotungstic acid hematoxylin stain. *C*, peroneal nerve just proximal to the swelling shown in *A*, showing loss of structure in center and beading at edges five days after stretch; Gros-Bielschowsky stain. *D*, peroneal nerve just proximal to swelling thirteen days after stretch (experiment 9).

In some bundles of nerve fibers the beading of axis-cylinders seen in lesser degrees of injury

tive lesion (fig. 2 *B* and *C*). Such myelin gaps were identical with those we have described in

the ischemic lesions produced by compression of nerve.[14]

In such lesions a thin myelin sheath was found to regenerate but the fibers remained in this state for one hundred and forty days in experiment 5. Though some collagenization remained at the site of damage, the condition was not such as to interfere with function.

*Pseudoneuroma and Neuroma Produced by Traction.*—If tension is continued after an increase in length of 100 per cent is obtained, the nerve does not suddenly rupture. Instead, there is heard a small, sharp noise, which may be described as a "crack" or a "snap," without any notable increase in extensibility. Close inspection of the peroneal nerve to determine the origin of this sound revealed that at one point a small white hernia had appeared on the side of the main nerve bundle. This most commonly occurred at about the junction of the upper and the middle third of the nerve. The herniation was evidently due to protrusion of the white nerve fibers through a longitudinal split in the perineurium. The split varied in length from 2 to 4 mm. There was no hemorrhage. If tension was persisted in, the whole nerve bulged out of the sheath at this point and the sheath threatened to rupture, becoming progressively thinner and slipping to one side of the nerve bundle. Further tension will lead to its final rupture, when the nerve fibers then begin to extend, not losing their continuity until long shreds are eventually pulled out.

The point at which the perineurium first ruptures and nerve fibers begin to herniate evidently marks the relief of a high internal tension within the tubular sheath. From that stage onward the resistance of the nerve to extension is much less.

Such an event always led to immediate complete paralysis. The smallest hernia thus obtained was allowed to remain one hundred and forty days. Recovery in function had commenced about the twenty-first day and was complete by the forty-eighth day. Nevertheless, at the end of the experiment a large pseudoneuroma was found on the nerve (fig. 3 *A*). On section this was found to consist of normal and regenerated nerve fibers separated by edematous tissue fluid (fig. 3 *B*, *C* and *D*). There was a moderate increase of endoneurial fibroblasts, with corresponding strands of collagen (fig. 3 *D*), but, except at the site of perineurial tear, no obstruction to regeneration had occurred. Most of the young regenerated fibers lay close to the former tear in the perineurium, indicating that the original damage to the axis-cylinders had been mainly at this point. Some axis-cylinders had entered the perineurial scar, there forming neuromatous whorls among the fibroblastic tissue. Not more than 2 per cent of fibers had been lost in this way. The condition was that which had been described as the "pseudo-neuroma" following percussion of nerve.[3] Distal to the swelling the nerve was thin for a distance, and in this region there was evidence of damage having occurred to some small epineurial vessels, which were then tortuous and had thickened walls and evidence of recanalization, with phagocytosis of some nearby blood pigment. Here, more nerve fibers had the thin sheaths of regeneration, and the few surviving large myelin sheaths showed gaps in their continuity (fig. 2 *B* and *C*). Edema of the nerve bundles and some beading of the original axis-cylinders, both proximal and distal to the pseudoneuroma and in its substance (fig. 3 *C*), were found.

An early stage of small herniation was also examined (experiment 7, table). The animal was killed on the fifth day. Rupture of epineurial vessels with thrombosis of small arterioles was found in two places in the epineurium left over the bulge. A transverse section (fig. 4 *B*) showed the loss of perineurium, of which one small last layer appeared to remain or to have been regenerated. Myelin sheaths next to the hernia had undergone complete dissolution, but the structure of the nerve remained intact. There was great congestion of the endoneurial vessels next to the opening, with some early proliferation of fibroblasts in this situation.

Section of a similar small hernia found in experiment 1, after thirteen days of survival, showed loss of perineurial structure with proliferation of fibroblasts and regeneration of nerve fibers through the opening (fig. 5 *A* and *B*). Phagocytes loaded with droplets of myelin had also been carried into the epineurium. Though the main bulk of nerve fibers remained intact, the small hernia, less than 1 mm. long, had evidently broken free of all perineurial restraint, with corresponding devastation in neural structure.

More pronounced herniation at the time of stretch induced severe damage to the nerve. In 1 such experiment, in which an opening 4 mm. long in the nerve and almost complete herniation of the contents through the opening had occurred.

14. Denny-Brown, D., and Brenner, C.: (*a*) Lesion in Peripheral Nerve Resulting from Compression by Spring Clip, Arch. Neurol. & Psychiat. **52**:1 (July) 1944; (*b*) footnote 13.

all the nerve fibers and myelin within the bulging hernia were found to be completely necrotic five days after the injury (fig. 4 *A*). The necrosis extended proximally in the center of the nerve trunk for 8 mm., leaving beaded axis-cylinders intact at the edge of the fasciculus (fig. 4 *C*). Throughout this region of damage to nerve fibers, fibroblasts and histiocytes were in active proliferation, and only occasional isolated surviving Schwann cells could be found. In the perineurial sheath in the proximal part of the swelling were an early fibroblastic proliferation and an inflammatory mononuclear and polymorphonuclear reaction.

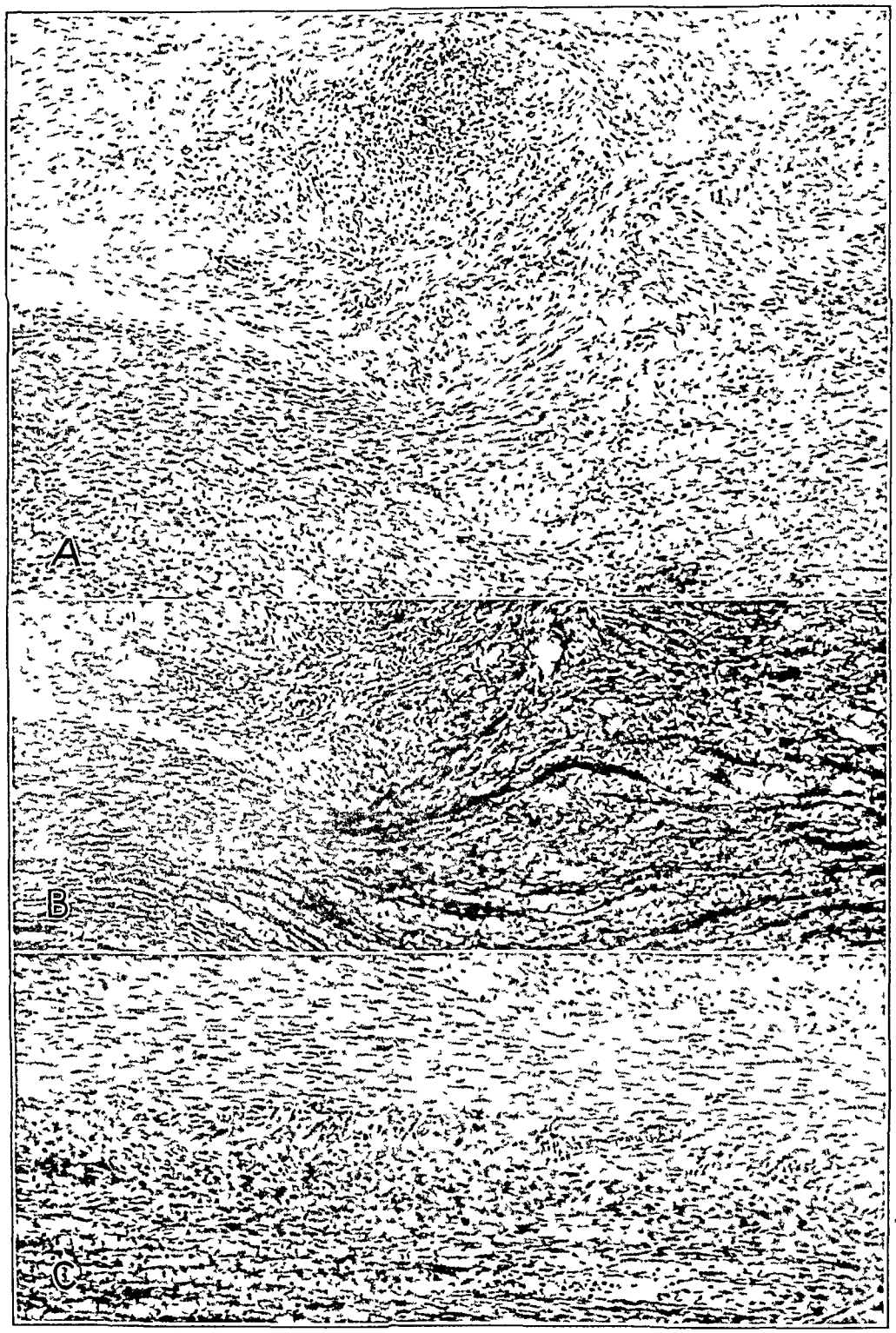



Fig. 5.—*A*, peroneal nerve, upper margin of a herniation through the perineurium thirteen days after stretch. The nerve bundle lies below, the herniated portion to the right. Hematoxylin and eosin stain. *B*, portion of the field shown in *A*; Gros-Bielschowsky method. *C*, perineurium lying between the epineurium (above) and a necrotic neural fasciculus (below). Note small capillaries running vertically between the two. Hematoxylin and eosin stain.

In another experiment a large herniation was allowed to persist for thirteen days before the animal was killed. The swelling here was entirely cellular and contained no trace of axis-cylinders, and only a few fragments of degenerated myelin remained (fig. 6*A*). The destruction of nerve fibers also extended medially in the center of the nerve for over 10 mm. (fig. 4*D*). The greater number of cells were neural fibroblasts, with oval, pale nuclei and active mitosis (fig. 6*B* and *C*), and the remainder were fat-filled phagocytes. The phosphotungstic

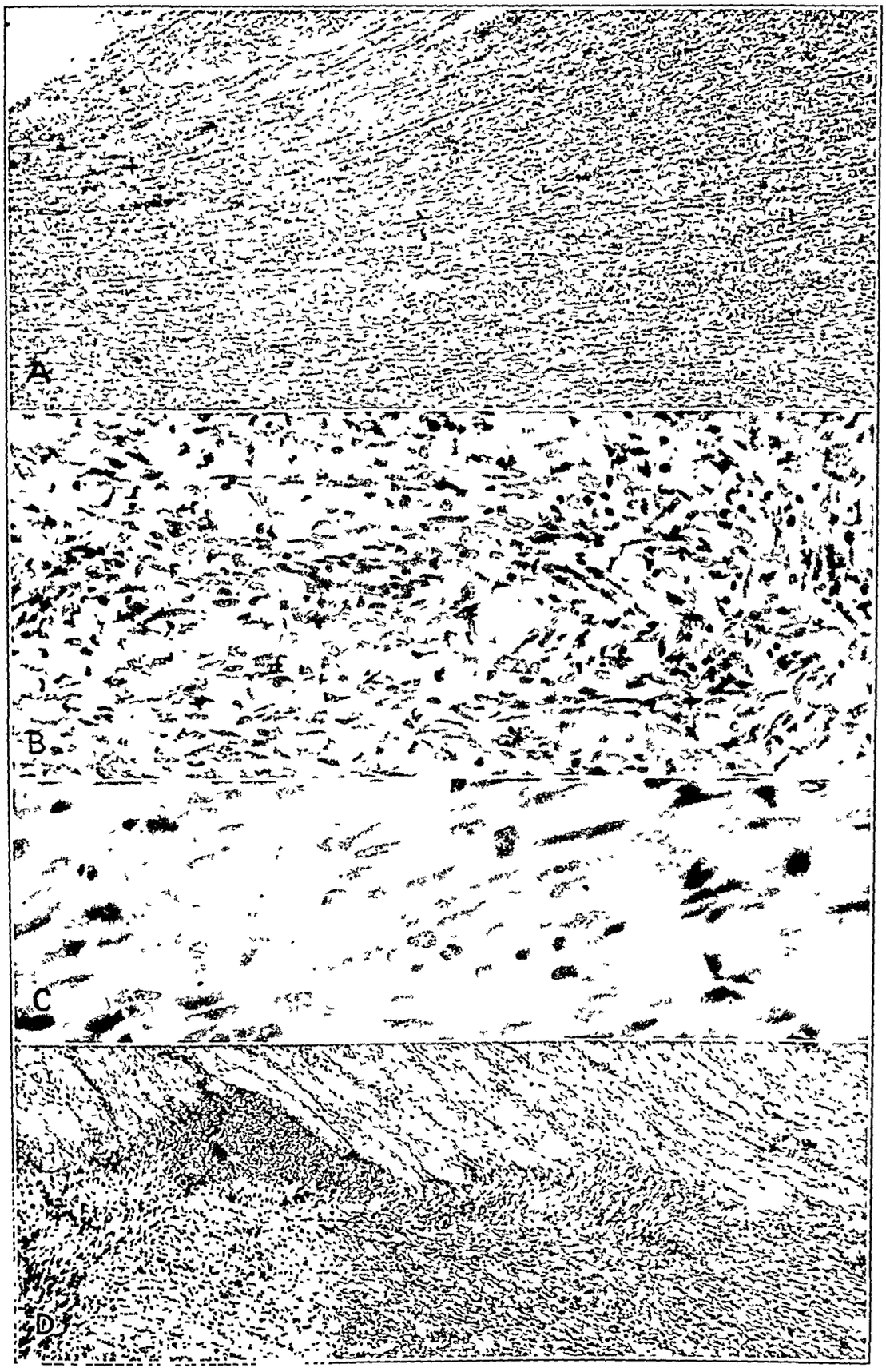



Fig. 6.—*A*, peroneal nerve, upper margin of a swelling thirteen days after injury (experiment 9), showing disappearance of myelin and the small amount of free fat; sudan III and hematoxylin stains. *B*, higher magnification of central part of neuroma shown in *A*, exhibiting loss of pattern; hematoxylin and eosin. *C*, higher magnification, to show nuclear detail and mitoses. *D*, from the same nerve as that shown in *A*, *B* and *C*, illustrating adherence to muscle at the edge of the fibroblastic mass; hematoxylin and eosin stain.

acid hematoxylin stain, which, as has been shown elsewhere (Denny-Brown [15]), is almost specific for Schwann nuclei, showed only two or three such nuclei in each section. Through three quarters of its circumference the cells of the herniated tissue were proliferating laterally among muscle fibers and the tendon aponeurosis (fig. 6 *D*), unlimited by the perineurium, which existed only in the remaining quarter. The structure of the nerve had been completely lost in this region. The swelling in this instance was therefore identical in structure with the central neuroma of a sectioned nerve, though maintaining direct continuity proximally and distally.

The nerve distal to the neuromatous bulge had also undergone dissolution, though the longitudinal collagenous tubes remained intact. The whole cellular swelling, and the central cone of the nerve just proximal and distal to it, showed complete disappearance of myelin and axis-cylinders, with intense phagocytosis. The more superficial parts of the nerves connected with the swelling, in which beaded fragments of axis-cylinders appear in figure 4 *D*, showed wallerian degeneration, in the form of fatty ovoids. The process of early dissolution of the axon and myelin in the swelling itself and the central parts of the connected nerves appeared to indicate ischemic necrosis of these structures. Only in the most peripheral part of the course of the nerve, before it entered the pretibial muscles, was normal wallerian degeneration generalized throughout the neural bundle. The intraneural and epineural veins were all greatly distended, and many of the small arterioles just distal to the herniation were occluded and tortuous. There was little hemorrhage, and this was limited to small punctate extravasations under the perineurium and in the epineurium. In some of the bundles of the nerve just distal to the swelling small capillaries appeared to enter the perineurium in great numbers (fig. 5 *C*), giving evidence of a collateral circulation to an ischemic segment. Regeneration was active in the segment of the nerve proximal to the swelling, but few fibrils had penetrated to the swelling, and these appeared then to lose direction and wander aimlessly.

This condition may therefore be described as the maximum degree of disorder of nerve in continuity. Though we have not had an opportunity to follow its development for long periods, there can be no doubt that it presents an obstruction to regeneration.

15. Denny-Brown, D.: Importance of Neural Fibroblasts in the Regeneration of Nerve, Arch. Neurol. & Psychiat., to be published.

## COMMENT

The experiments that have been cited indicate that the peripheral nerves have some physiologic extensibility. The degree of extension which can be obtained with large trunks, such as the sciatic nerve, is small but increases in the smaller fasciculi. Segments of the peroneal nerve of the cat can extend to nearly 100 per cent of their resting length without damage. With such extensions, some of the larger axis-cylinders become beaded in appearance, and the incisures of Schmidt and Lantermann in the myelin sheath are lengthened. Identical beading can be produced by tension in the dead but unfixed axis-cylinder by longitudinal tension. We have taken precautions to avoid such artefact in the present experiments and would comment only that this phenomenon must have a physical basis, for it can be reproduced in an elastic tube filled with plastic substance.

These changes persisted as long as five months after the stretch, indicating a plastic rather than an elastic structure. We regard this feature and the similar persistence of the deformities of the axon induced by edema previously described [14a] as being strong evidence against the hypotheses which postulate a normal flow of axonic fluid within an axonic membrane, a "turgor pressure" (Young [16]) or reproduction of a basic neural substance near the nucleus of the nerve cell (Weiss [17]).

Further extension of the nerve interferes with both structure and function by tearing the smaller epineurial vessels. This leads to damage to nerve fibers by ischemia, producing patchy edema, or intermediate degrees of the ischemic lesion, with loss of segments of the myelin sheaths, or small areas of complete degeneration. The degree of stretch at which such changes occur is not easy to determine except that petechial hemorrhages in the epineurium indicate that a major degree of the disorder has occurred. The neural degeneration thus produced is recoverable without complication, and no evidence of obstruction was obtained. The level at which damage occurred was not constant and evidently corresponded to some variability in tensile strength of the epineurial fibrous and elastic tissue. The insertion of the nerve into muscle was not found to be a particularly vulnerable point.

Of greater interest was the demonstration that stretching a nerve could produce a swelling in

16. Young, J. Z.: Contraction, Turgor, and the Cytoskeleton of Nerve Fibers, Nature, London **153**: 333, 1944.

17. Weiss, P.: Evidence of Perpetual Proximo-Distal Growth of Nerve Fibers, Biol. Bull. **87**:160, 1944.

continuity, for the causation of such swellings in clinical nerve lesions has been in some doubt. The mechanism of the swelling was traced to an initial rupture of the perineurial sheath, an event which makes its first appearance as a longitudinal split, through which the contents immediately herniate as if under great internal pressure. The degree of herniation determined the subsequent fate of the nerve at this point. The small hernias retained a thin superficial layer, probably a last internal lamina of perineurium, which appeared to preserve the general structure of the neural fasciculus. There was, nevertheless, evidence of damage to endoneurial blood vessels, which became greatly congested at this point. The subsequent course of such a swelling indicated

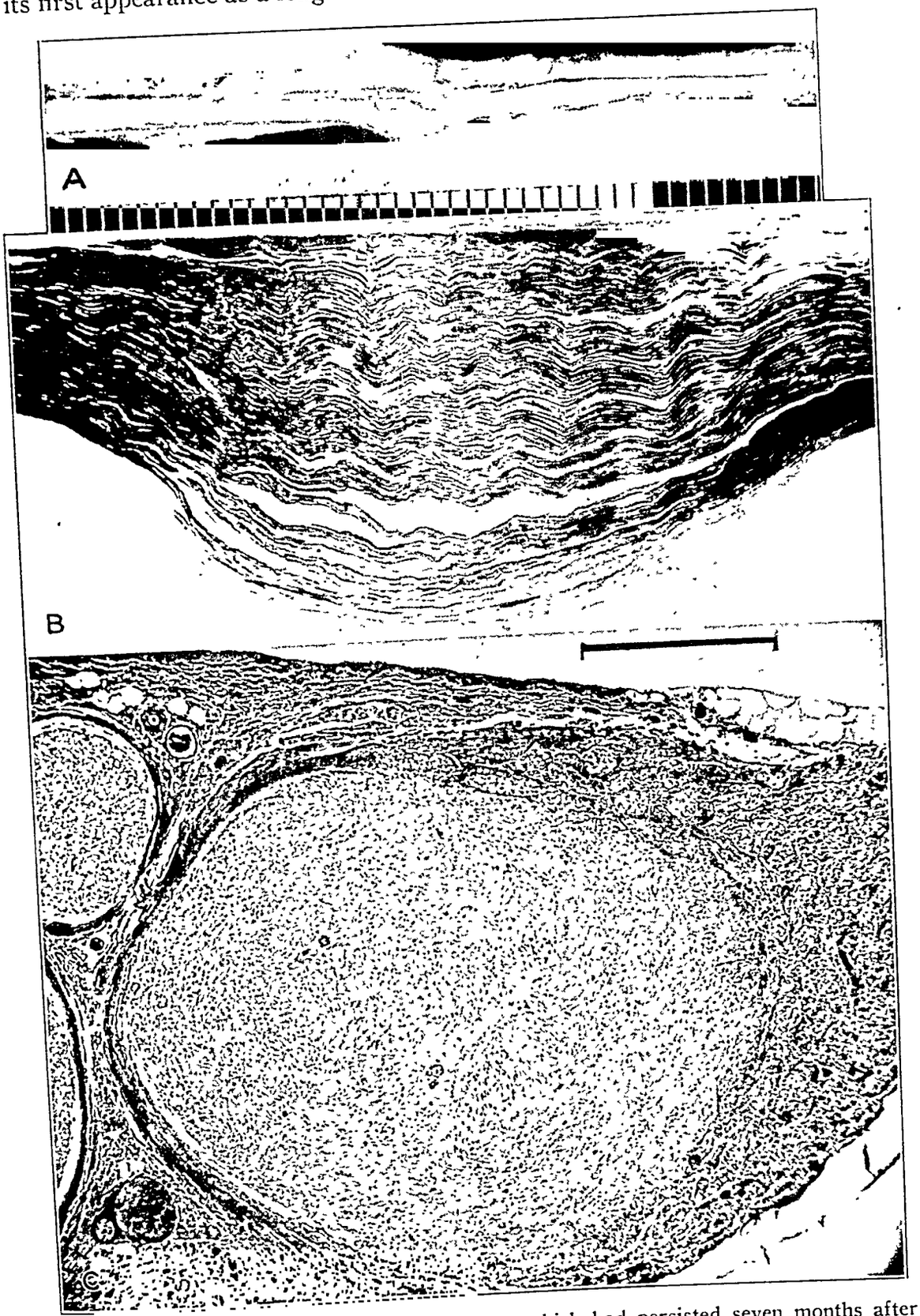



Fig. 7.—Sciatic nerve of cat, showing a pseudoneuroma which had persisted seven months after a percussion causing transient paralysis, of less than six weeks. *B*, longitudinal section of one of the nodules, showing myelin sheaths. The myelin sheaths are paler (regenerated) in the distal part of the swelling (right). Spielmeyer method. *C*, transverse section of one of the nodules, showing reconstitution of the perineurium. The ruled line in the upper corner corresponds to 0.5 mm. Hematoxylin and eosin stain.

efficient repair of the hernia through regrowth of the perineurium. A few superficial fibers became caught in the scar, but the bulk of the nerve retained normal structure. After approximately five months the swelling still remained, though the nerve had regained full motor function by the forty-eighth day and histologically was efficiently regenerated. The swelling was seen to be due chiefly to a local increase of endoneurial fluid. Some increase of endoneurial cells with mild deposition of collagen had occurred, but there was no indication that this was a progressive change. The condition is identical with that which we have found to result from percussion of nerve, and which might be called "benign pseudoneuroma." Since we reported the production of such swellings by percussion, we have seen examples of this swelling persist as long as seven months (fig. 7) without deterioration of function. The perineurium was found to have been reconstituted, though not without enmeshing some bundles of nerve fibers (fig. 7 *C*). The loss of fibers was very small, as can be seen in figure 7 *B* and as was confirmed with stains for axis-cylinders.

The source of the intraneural fluid in such circumstances is open to speculation. The vascular supply of the region has long since been reconstituted, so that continued venous congestion is not an adequate cause. There is no evident obstruction of any supposed circulation of intraneural fluid, for the tissue spaces merge imperceptibly into those proximal and distal to the injury. The obstruction is at the point of damage, not proximal or distal to it. We have to conclude that once highly albuminous fluid collects within endoneurial spaces its removal is an extremely slow process. The patches of "edema" which we have found in lesser degrees of injury from stretching, and then clearly related to damage to small blood vessels in the epineurium (fig. 2 *D* and *E*), are of identical nature, and for this reason we are inclined to believe that the fluid was originally a transudate associated with tissue damage. We have previously noted the early formation of such edema as a result of percussion with an intact perineurial sheath [3] and as a result of simple obstruction of the neural blood vessels without loss of function.[14a]

After a large herniation, both the hernia and the center of the neural fasciculus for a distance proximal and distal to it showed rapid dissolution of both myelin and axis-cylinders. This process was much more rapid than wallerian degeneration, and, in view of its occurrence under conditions of persistent severe but incomplete ischemia,[14a] we feel that it can be attributed to the accompanying dislocation and rupture of small blood vessels. More important in ultimate effect are a widespread proliferation of endoneurial fibroblasts within the swelling and their diffusion into neighboring tissues. The nerve loses its structure at this level and is converted into a solid neuroma.

In another place [15] we have presented evidence that the endoneurial cells are in the nature of fibroblasts, which respond to all manner of injury with multiplication, and that the natural function of the flat mesothelial cells of the perineurium restrains this proliferation. The present experiments indicate that the difference between the benign pseudoneuroma and the true spindle neuroma is related to the degree of disorganization of the architecture of the nerve bundle, and this, in turn, to the extent of fibroblastic proliferation.

It has been shown that stretch of nerve can produce all gradations between simple pseudoneuroma and spindle neuroma. The determining factor was the extent of initial rupture of the perineurium and the degree to which repair of that membrane controlled endoneurial fibroblastic proliferation. We have found that after transverse section of nerve the few fibroblasts in the perineurium join those of the endoneurium in the formation of scar tissue. The present experiments indicate that after small tears in the perineurium the flat mesothelial cells can repair the gap, although fibroblasts are also entangled in them.

We have already alluded to the work of Black, Burns and Zuckerman [4] in demonstrating the tissue tensions which arise with penetrating injuries from high velocity projectiles. From this, there is no doubt that powerful and extremely rapid stretching of nerves near the path of such a projectile must be a common event. We feel that the high frequency of intraneural fibrosis found to result from such injuries must be due to perineurial rupture of the type here described.

The nodule which forms a pseudoneuroma is similar in size and general shape to that of a true neuroma. It is of importance for the surgeon to be able to distinguish the benign edematous swelling from the fibrous scar with loss of endoneurial structure. Both feel firm and resistant. The true neuroma should be adherent to surrounding structure: the pseudoneuroma, of smooth and unbroken surface. Unfortunately, however, the initial injury, especially if due to a high velocity projectile, often results in extraneous scar tissue, which closely surrounds the nerve and obscures observation of its perineurium. A test of perineurial continuity would

therefore appear to be necessary. Injection of saline solution along the neural fasciculus appears rational, and the method has been frequently used. It is open to the objection that if too great force is used, rupture of the internal structure of the bundle and small vessels will be caused. Until some other method, such as the use of a vital dye to stain the scar, has been developed, injection of saline solution remains the only method generally applicable.

## SUMMARY AND CONCLUSIONS

The effects of stretching a peripheral nerve beyond the limit of physiologic elasticity are related to the degree of extension thus produced. In milder degrees of stretch there occurred damage to epineurial vessels, with resultant patches of ischemic changes in nerve fibers. In more severe injuries the perineurium was ruptured and the nerve bundle herniated.

After the milder purely ischemic lesions there was efficient regeneration. Recovery following rupture of the perineurium varied in proportion to the extent of herniation of endoneurium immediately following injury.

After mild herniation of perineurial contents the perineurium was repaired. A pseudoneuroma formed and persisted for as long as five months without impairing almost complete regeneration of the nerve fibers. The swelling was due chiefly to the presence of fluid in the endoneurial spaces.

After severe herniation through the perineurium the nerve fibers in the swelling, and for a distance on either side, underwent necrosis. This damage was probably the result of the related vascular damage. The endoneurial fibroblastic tissue then proliferated in the manner of a neuroma, soon obliterating all trace of the original structure of the nerve at the level of the swelling, which thus became a true neuroma.

The ballistics involved in injuries to the limbs by high velocity projectiles are such as to induce stretch injuries to nerves at a distance from the track of the projectile and thus to lead to lesions in continuity.

Boston City Hospital (18).

# THE CENTRAL NERVOUS SYSTEM IN UREMIA

## A CLINICOPATHOLOGIC STUDY

JULIAN KNUTSON, M.D., AND A. B. BAKER, M.D.
MINNEAPOLIS

Uremia, because of its frequent renal origin, has been a subject of investigation primarily of the internist. For this reason, the greatest emphasis in the more recent literature has been placed on the renal and chemical aspects of this disease in spite of the fact that some of the most outstanding symptoms are neuropsychiatric in nature. The most common complaints referable to the nervous system are convulsions and coma. Addison,[1] as early as 1839, characterized the cerebral symptoms as "dullness of the intellect, sluggishness of manner, drowsiness going on to quiet stupor and ending in coma, often with convulsions." Although these are the better recognized forms of cerebral symptoms, a careful survey of a large series of cases will demonstrate almost every type of neuropsychiatric involvement, from the purely ascending motor disturbances to the full-blown psychoses of almost every type. The significance of the cerebral involvement which occurs in this illness was well recognized by the clinicians of a half-century ago, but this aspect of the problem has almost entirely disappeared from the recent literature. It was for the purpose of again emphasizing the clinicopathologic aspects of the effect of uremia on the central nervous system that the present study was undertaken.

It has long been recognized that uremia produces definite tissue changes within the central nervous system. The extreme importance of such changes was emphasized by the occasional occurrence of a striking chemical improvement in respect to nitrogenous metabolities of the blood, associated with a stubborn persistence of the various clinical symptoms, particularly those related to the nervous system. Because of the frequent predominance and severity of neuropsychiatric symptoms in this disease, many of the earlier investigators studied the brain in fatal cases to determine the nature of the occurring lesions. As a result of these investigations, descriptions of a wide variety of lesions accompanied with numerous individual interpretations have appeared in the older literature. The most prominent findings have been described as occurring within the cerebral cortex, although almost every part of the nervous system has been implicated. The chief histopathologic alterations associated with uremia seemed to involve the cortical neurons. Such changes have been reported by Bodechtel,[2] Hechst,[3] Rives,[4] Hiller and Michalovici,[5] Uchida,[6] Grinker,[7] Weiman,[8] Weil[9] and Mikuriya.[10] The cell changes were most variable in degree and in distribution. Most commonly, there occurred an irregular loss of tinctorial properties involving scattered elements of the various cortical areas, chiefly the third and fifth laminas. (Bodechtel,[2] Hechst,[3] Rives[4]). In some cases this tinctorial loss was severe, producing actual foci of devastation (Hechst[3]). In the cases of acute type the cortical neurons frequently revealed severe swelling with partial or complete chromatolysis (Hechst,[3] Hiller and Michalovici,[5]

From the Department of Neuropsychiatry, University of Minnesota Medical School (Dr. Baker).

This study was aided by a grant from the Research Funds of the Graduate School of the University of Minnesota.

1. Addison, T.: A Collection of the Collected Works of Thomas Addison, edited by Wilks and Daldy, London, New Sydenham Society, 1868.

2. Bodechtel, G.: Hirnveränderungen bei den verschiedenen Formen der Urämie unter Berücksichtigung ihrer Pathogenese, Deutsches Arch. f. klin. med. **174:** 541-569, 1933.

3. Hechst, B.: Ueber Gehirnbefunde bei urämischen Zuständen, Ztschr. f. d. ges. Neurol. u. Psychiat. **139:** 544-588, 1932.

4. Rives, J.: Lesions architéctoniques de l' ecorce cérébrale chez les urémiques convulsifs et dans la sénilité, Folia neuropath. **1:**96-104, 1923.

5. Hiller, F., and Michalovici, E.: Lésions organiques cérébrales au cours de l'urémie, Schweiz. Arch. f. Neurol. u. Psychiat. **46:**203-215, 1941.

6. Uchida, K.: Pathologisch-anatomische Untersuchungen an Gehirnen nach Urämie, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **31:**37-54, 1929.

7. Grinker, R.: Neurology, ed. 3, Springfield, Ill., Charles C Thomas, Publisher, 1943, pp. 656-658.

8. Weiman, W., in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, pp. 84-86.

9. Weil, A.: Textbook of Neuropathology, Philadelphia, Lea & Febiger, 1933.

10. Mikuriya, J.: Hirnveränderungen bei der Urämie, Fukuoka acta med. **32:**107-108, 1939.

Uchida,[6] Grinker,[7] Weiman[8]). Occasionally the damage to the nerve cells was much more severe and consisted of vacuolation (Uchida,[6] Hechst[3]), pyknosis (Weiman,[8] Weil[9]) or even fatty degeneration (Weiman,[8] Weil,[9] Hechst[3]).

Although the neuronal changes appeared to be the most consistent alteration, numerous other changes were observed within the cortex. Hechst[3] reported scattered foci of softening, while both Hechst[3] and Bodechtel[2] observed scattered areas of bleeding. The various investigators differ in their observations regarding the glial elements within the cortex. In some cases there was a mild astrocytic increase, which was perivascular (Hechst[3]) or diffuse (Mikuriya[10]). Mikuriya also observed numerous glial nodules within the cortex in some of his cases. Hechst, on the other hand, described degeneration and necrosis of the glial elements around many of the cortical blood vessels.

Alterations have also been reported within the cerebral white matter, involving both the myelin and the glial elements. The demyelination was usually focal in nature (Hechst,[3] Weil[9]) and in many cases was strictly localized to the perivascular regions (Grinker,[7] Hiller and Michalovici[5]). The glial changes were most variable and were both degenerative and proliferative. Weil[9] and Weiman[8] observed widespread destruction of the perivascular glia, while Bodechtel[2] and Hiller and Michalovici[5] reported astrocytic proliferation. Bodechtel[2] stated the belief that the glia proliferated focally to form nodules in cases of true uremia, while in cases of pseudouremia this gliosis was of a more diffuse nature. Mikuriya[10] observed no differences in the nature of the astrocytic increase in the different types of uremia.

These tissue changes, although most commonly observed within the cerebral hemispheres, also appeared in other parts of the central nervous system. The brain stem was frequently involved, producing extensive alterations within the cranial nerve nuclei (Hechst,[3] Weil,[9] Mikuriya,[10] Silvan[11]). Silvan[11] found that most of the damage in his case was limited to the bulbar region and the reticular formation and that the changes were correlated accurately with the clinical findings. The neuronal damage was often selective, involving the nucleus of the vagus nerve while sparing other nuclei in the same region, such as the hypoglossal. Mikuriya and Hechst reported areas of softening within the pons. Weil, Hechst and Mikuriya observed striking alterations within the basal ganglia. Hechst observed neuronal damage and large areas of softening, while Mikuriya found vascular changes with hyperemia and numerous petechial hemorrhages. Pontile lesions were described by Mikuriya,[10] Hechst[3] and Weil,[9] while definite, and often extensive, cerebellar alterations were reported by Hechst,[3] Weiman[8] and Weisenburg.[12]

A great deal of emphasis has been placed by many of the earlier workers on the vascular alterations and the changes within the choroid plexus. The nature of the vascular changes has been most variable. Hechst,[3] Hiller and Michalovici[5] and Pollak and Rezek[13] described chiefly a vascular congestion with scattered perivascular and petechial hemorrhages. Changes within the vessel walls have been recorded by many investigators (Boedechtel,[2] Hechst,[3] Weil,[9] Pollak and Rezek[13]). These vascular changes were variable. In some cases there occurred merely a splitting of the elastica interna (Hechst[3] Pollak and Rezek[13]), while in other cases actual hyaline and calcium alterations were reported (Hechst,[3] Weil[9]). Often extensive vascular damage resulted, with actual necrosis of many of the elements of the wall (Pollak and Rezek,[13] Bodechtel[2]). Perivascular edema was reported by Hechst[3] and Pollak and Rezek.[13]

The role played by the choroid plexus in the production of uremic symptoms has been the subject of much speculation. Von Monakow[14] found that the cerebral symptoms of uremia appeared suddenly, even though the changes in the blood and the degree of uremia remained unaltered. Because of this, he concluded that the cerebral symptoms could not be caused entirely by the toxic products within the blood but, rather, were due to some factor which allowed the toxins to act on the brain. He felt that the choroid plexus was primarily engaged in holding back the toxins and when they finally became severely altered they allowed the toxins to pass through to the brain, resulting in the sudden onset of symptoms. Because of the possible role played by the choroid plexus in uremia, many extensive studies have been made to find alterations within these structures

11. Silvan, C.: Contributo allo studio dell' anatomia patalogica del sistema nervosa nell' uremia in un caso simulante paralisi del vago, Riv. di pat. nerv. **17**:410-424, 1912.

12. Weisenburg, T. H.: Uremic Hemiplegia with Changes in the Nerve Cells of the Brain and Cord and Recent Primary Tract Degeneration of One Central Motor Tract, J. Nerv. & Ment. Dis. **31**:456-464, 1904.

13. Pollak, E., and Rezek, P.: Studien zur Pathologie der Hirngefässe, Virchows Arch. f. path. Anat. **269**: 254-279, 1928.

14. von Monakow, P.: Urämie und Plexus Choroidei, Schweiz. Arch. f. Neurol. u. Psychiat. **13**:515-525, 1923.

in this disease. Many changes have been reported. The epithelium of the choroid villi has been observed to be either desquamated or greatly swollen and vacuolated (von Monakow,[14] Tannenberg,[15] Saito[16]). Granules often were present within the cell cytoplasm, giving the latter a thickened appearance (Saito[16]). The connective tissue around the vessels appeared proliferated, resulting in papillary widening. In contrast to these changes, two investigators (Bodechtel[2] and Hechst[3]) found no alterations within the choroid plexus which could not be accounted for by the age of the patient.


Fig. 1 (case 1).—Cerebral cortex. (*A*) The nerve cells are slightly swollen and show partial irregular chromatolysis. (*B*) Ghost cell formation. Two of the nerve cells have lost most of their tinctorial properties. A faint outline of some of the Nissl granules can still be seen within these cells. Nissl stain.

We have had the opportunity of studying in detail the tissues in 12 cases of fatal uremia and have selected 5 of these for presentation in the present report. In the latter group, the illness was fairly acute in 1 case and moderately or definitely prolonged in the others. Since the duration of the uremic process seemed to be the most important factor in determining the severity of the cerebral changes, we felt that such a selection of cases would offer a better opportunity to trace carefully the development of the pathologic alterations within the nervous system and to correlate such changes with the clinical symptoms. For the pathologic studies, blocks were taken from areas throughout the nervous system and were prepared for study by the following technics: hematoxylin and phloxine stain, Nissl's stain (thionin), the Weigert–Van Gieson stain for blood vessels, Bodian's stain for axons, Pal-Weigert's and Weil's stains for myelin sheaths and Cajal's gold chloride-mercury bichloride impregnation method for astrocytes.

## REPORT OF CASES

CASE 1.—A 5 month old child had acute extrarenal uremia. Autopsy revealed acute changes in the nerve cells involving chiefly the cortex and the brain stem. Early perivascular demyelination and mild perivascular bleeding were present within the cerebral white substance.

*History.*—S. A., a 5 month old girl, was brought to the hospital on Dec. 12, 1941 because of severe diarrhea, which had been present for one week. The baby was more irritable than usual on the morning of admission, at which time her temperature was 102 F. Vomiting was present.

On admission to the hospital the infant was in extremis. She was extremely cyanotic, and her respirations were shallow and infrequent. Her body was hot, but the extremities were cold. The temperature was 106 F. Her eyes were glassy and dull; the lips were

15. Tannenberg, J.: Ueber Plexusveränderungen und Beziehungen zur Urämie, Centralbl. f. allg. Path. u. path. Anat. **32**:169-176, 1921.

16. Saito, M.: Zur Pathologie des Plexus choroideus, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **23**:49-90, 1922.

dry, and the neck was flaccid. The breath sounds were obliterated by mucus in the throat. The heart tones were inaudible. The blood urea nitrogen measured 71 mg. per hundred cubic centimeters, and the carbon dioxide-combining power was less than 3 volumes per cent. Oxygen was started immediately, and the baby rallied for a few moments, with slight decrease in the degree of cyanosis. An attempt was made to start intravenous injection of fluid, but less than an hour after admission the patient died.

Fig. 2 (case 1).—Cerebellum. The Purkinje cells are greatly swollen. Most of their processes are absent, giving the cells a rounded appearance. Nissl stain.

*Autopsy.*—The body was that of a poorly nourished white female infant. The lungs showed a few areas of atelectasis, and the posterior portions were congested. There were four areas of intussuception in the small intestine, which probably represented agonal change. The other organs were normal. Gross examination of the brain revealed a relatively mild brownish pigmentation disseminated over the surface of the brain. The cerebral cortex was congested and contained scattered perivascular extravasations.

*Microscopic Examination of Brain.*—The gray matter of the hemispheres revealed scattered changes within the nerve cells, consisting primarily of mild swelling and partial or complete chromatolysis (fig. 1 *A*). Some of the cells had completely lost their ability to stain and appeared as ghost cells (fig. 1 *B*). The cell processes often were detached, producing a swollen, rounded appearance. The nuclei, as a rule, were uninvolved. These neuronal changes showed a distinct tendency to be patchy, with the involved elements surrounded by large groups of structurally intact cells. On cursory examination the subcortical tissues appeared unchanged. However, the special stains revealed early focal changes in the myelin, consisting chiefly of slight swelling of the sheaths. The axons within these areas showed no structural changes.

The nerve cells within the basal ganglia revealed moderate diffuse chromatolysis but no nuclear changes. The smaller arteries were congested and occasionally surrounded by distended perivascular spaces containing erythrocytes.

The cerebellum was extensively involved. Many of the Purkinje cells had lost most of their tinctorial properties and were difficult to outline adequately. The cells that did accept the stain appeared swollen, and their processes were fragmented or even absent (fig. 2).

Acute changes in the nerve cells were present within scattered regions of the brain stem, implicating chiefly the descending roots of the trigeminal nerves, the hypoglossal and the medial vestibular nuclei and the nuclei solitarii. The involved neurons showed chiefly pronounced swelling and chromatolysis but no nuclear alterations.

Case 2.—A man aged 36 entered the hospital with complaints of visual disturbance, nausea and vomiting. The blood urea nitrogen measured 220 mg. per hundred cubic centimeters. He died within twenty-four hours, during a convulsive seizure. Autopsy revealed acute and chronic changes in the nerve cells, involving chiefly the cerebral cortex and the brain stem. There were scattered areas of perivascular and focal demyelination in various stages of alteration and repair.

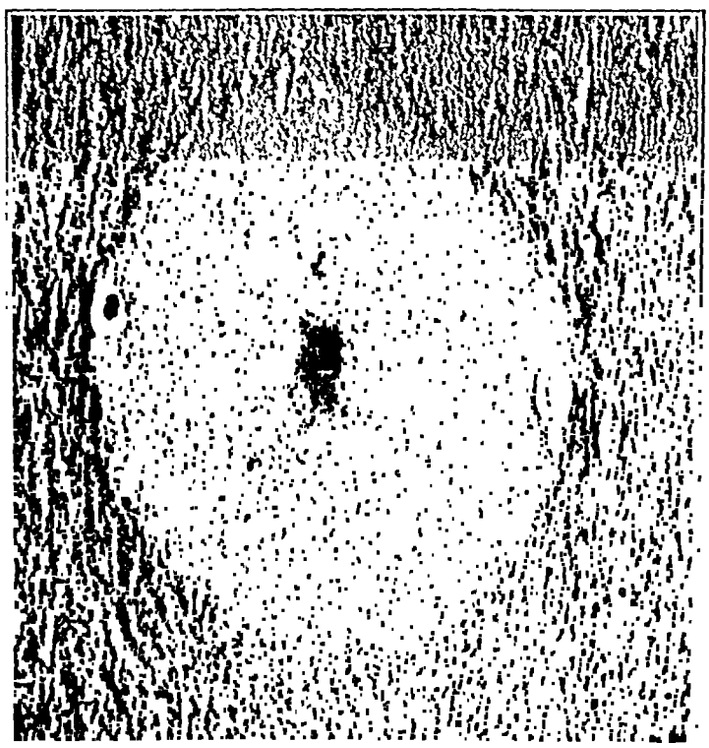


Fig. 3 (case 2).—Perivascular demyelination within the white matter. The involvement is almost complete and is sharply circumscribed. Pal-Weigert stain.

*History.*—E. G., a 36 year old farmer, entered the hospital on Nov. 2, 1943. Ten months previously he was first told that he had high blood pressure. In July he noticed some difficulty with vision. Two weeks prior to admission, nausea developed, and he had occasional periods of vomiting. Spontaneous epistaxis began the morning of admission.

Examination revealed that the patient was dyspneic, slightly lethargic and uncooperative. A systolic murmur was heard at the apex, and the aortic second sound was accentuated. Pitting edema was present over both ankles. The urine had a specific gravity of 1.010 and

contained albumin, some red blood cells and many white blood cells. The blood urea nitrogen measured 220 mg.; the cholesterol, 246 mg.; the calcium, 11 mg., and the phosphorus, 14.8 mg., per hundred cubic centimeters.

The patient failed rapidly in spite of oxygen, diuretics and attempted rapid digitalization. He died twenty-four hours after admission, after a generalized clonic convulsion.

*Autopsy.*—About 30 cc. of fluid was present in the pleural cavities. The lungs were edematous and congested. The kidneys were small; the right weighed 130 and the left 115 Gm. There was fine pitting of their external surfaces, and on section the cortices were narrowed and yellowish. Gross examination of the brain showed some fibrosis of the meninges in the region of the hypothalamus. Coronal sections revealed sparsely disseminated petechiae throughout the cerebrum, especially in the white substance.

*Microscopic Examination of Brain.*—The cerebral cortex showed numerous changes, involving both the cellular and the interstitial elements. The cortical neurons were irregularly but diffusely involved throughout both cerebral hemispheres. The most frequent alteration consisted of diffuse chromatolysis, often associated with nuclear changes. The cell nuclei were often situated eccentrically and revealed definite changes in shape, size and membrane structure. In a few neurons the processes were definitely swollen and even fragmented. Aside from these changes in the nerve cells, there were many striking tissue alterations. Many of the cortical vessels were surrounded by distended perivascular spaces or areas of definite demyelination. Scattered areas of softening apparently unassociated with the vessels were also observed. In some cases these softened areas had resulted in tiny cavity formations already surrounded by a mild glial scar.

The white matter exhibited scattered areas of demyelination, most of which were perivascular in distribution (fig 3). In addition, there were observed numerous small foci of necrosis filled with fat granule cells. A diffuse glial increase was noted throughout the white matter.

The thalamus revealed chronic changes. There was an apparent decrease in the number of neuronal elements. Many cells were shrunken and pyknotic. Areas of old tissue injury with resultant vacuolation were observed near the walls of the third ventricle.

The brain stem also revealed neuronal and interstitial changes. Many of the cells of the facial nuclei were chromatolytic and vacuolated and even showed a nuclear loss. The cells of the mesencephalic root of the trigeminal nerve showed acute swelling associated with perinuclear chromatolysis. This entire nucleus was almost completely destroyed, hardly a normal cell remaining. Similar swelling and chromatolysis appeared in many of the neurons within the pontile nuclei. Focal areas of demyelination occurred in the region of the trapezoid body. Numerous glial nodules were scattered throughout the brain stem. The vessels were structurally uninvolved.

CASE 3.—A 26 year old housewife, with a history of renal trouble since infancy, had had diarrhea and vomiting for one month. The blood urea nitrogen level was 254 mg. per hundred cubic centimeters on her admission and dropped to 50 mg. per hundred cubic centimeters with treatment. Convulsions appeared in spite of improvement in laboratory findings. Autopsy revealed widespread devastation of the neurons and extensive myelin changes, involving all areas of the brain.

*History.*—R. B., a 26 year old housewife, entered the hospital on Dec. 14, 1943, with a history of diarrhea and vomiting of one month's duration. She had had nocturia during this time but no dysuria, hematuria or pyuria. She had had renal trouble since the age of 2 years, the disorder following scarlatina.

Examination revealed that the patient was well nourished and well oriented. Her mouth contained ulcerated areas over both buccal regions and under the tongue. There was slight pitting edema over both tibias. The urine had a specific gravity of 1.010. The blood urea nitrogen level was 254 mg. per hundred cubic centimeters; the carbon dioxide–combining power was 27 volumes per cent, and the chlorides measured 572 mg. per hundred cubic centimeters. Phenolsulfonphthalein tests showed a total excretion of 3 per cent at the end of two hours.

Fig. 4 (case 3).—Focal and perivascular areas of demyelination. The changes are very early and are fairly well localized. Weil stain.

Although the patient's acidosis was readily corrected by administration of saline solution and the high level of urea nitrogen was reduced to 50 mg. per hundred cubic centimeters, the patient failed to improve clinically. In spite of an almost normal urea nitrogen level, about one week after admission she suddenly had her first convulsion. The convulsions were chiefly of a grand mal type and were preceded by a cry and followed by long periods of unconsciousness. In the intervals between the attacks, her muscles would twitch and her arms would jerk in an irregular manner. The convulsions increased in frequency, and the patient gradually became confused and disoriented and died Jan. 7, 1944.

The creatinine level of the blood was 6.9 mg. per hundred cubic centimeters on December 20, and two days later it had risen to 190 mg. The neurologic examination on December 25 revealed the pupils to be dilated but reactive to light and in accommodation. A

vertical nystagmus was present. The fundi were normal. The deep reflexes were normal. A Babinski sign was present on the right.

*Autopsy.*—There was edema of the face, eyelids and ankles. A few petechial hemorrhages were present over the abdomen. Gross examination of the brain revealed definite vascular congestion. This was most marked in the parieto-occipital region.

*Microscopic Examination of Brain.*—There was widespread devastation of the neurons in scattered areas throughout the cortex. Many of the cells were only mildly involved, showing only swelling and chromatolysis. Others were more severely damaged, resulting in marked tinctorial loss, vacuolation and even pyknosis.

Within the mesencephalon, the neurons of the oculomotor nucleus were widely involved. Scattered areas of perivascular demyelination were present within the substantia nigra. The nuclei of the vagus nerves were also diffusely involved, with most of the cells revealing either diffuse chromatolysis or early pyknosis. The ganglion cells of the spinal vestibular nuclei were pyknotic.

CASE 4.—Recurrent attacks of motor weakness occurred over a period of one year. The final attack appeared as an ascending paralysis, terminating fatally with bulbar palsy. The blood urea nitrogen measured 210 mg. per hundred cubic centimeters. Autopsy revealed both acute and chronic neuronal changes within

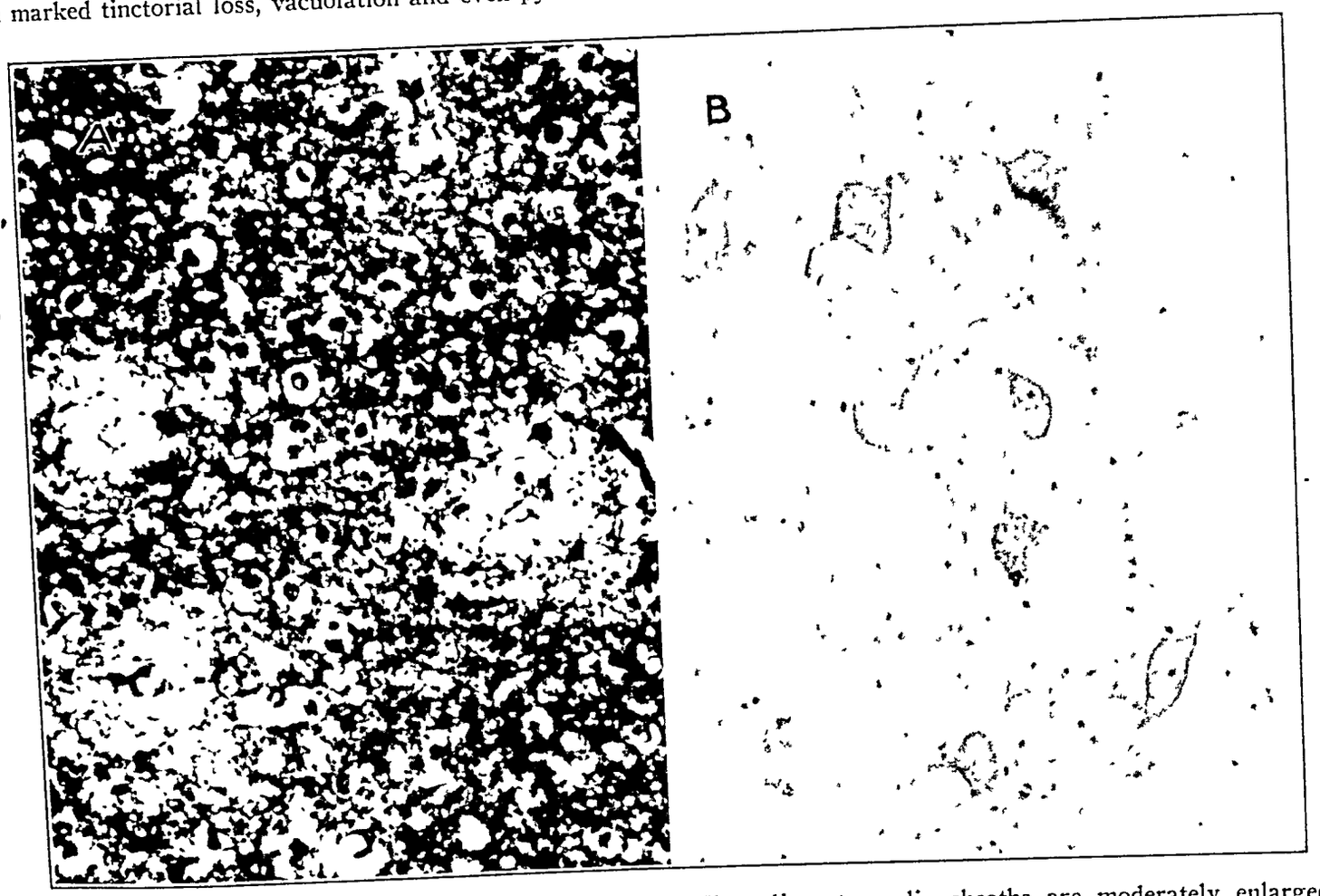



Fig. 5 (case 4).—*A,* small focal areas of demyelination. The adjacent myelin sheaths are moderately enlarged. Weil stain. *B,* anterior horn of the spinal cord. The cells show some swelling and extensive chromatolysis. Many of the cell processes have disappeared. Nissl stain.

Isolated areas of softening, filled with scavenger cells, were observed.

The white matter exhibited conspicuous focal and perivascular demyelination (fig. 4). In scattered lesions early cavitation appeared, surrounded by an irregular glial wall. These lesions obviously indicated a more chronic process. Small ball hemorrhages were noted. The walls of many of the smaller vessels when stained with special methods appeared frayed and often stained irregularly. Occasionally small ball hemorrhages were observed in the vicinity of such altered vessels. The globus pallidus exhibited widespread neuronal changes, consisting chiefly of chromatolysis. Early focal myelin damage was also visible. A diffuse glial increase was present.

Many of the Purkinje cells of the cerebellum had disappeared. Many of the remaining cells were altered, revealing diffuse chromatolysis or complete loss of their staining properties. The larger blood vessels of the cerebellum presented some thickening of the media. the cortex and the nuclei of the brain stem. Numerous areas of perivascular and focal demyelination were observed within the white matter.

*History.*—A. H., a 45 year old farmer, was admitted to the hospital April 11, 1944, after having accompanied his daughter to the clinic, where she was undergoing investigation for pituitary basophilism. Apparently, he had been well until that forenoon, when there suddenly developed vomiting and a staggering gait. At this time he noticed weakness in his legs. This paresis ascended to involve the proximal muscles of his shoulders. His limbs rapidly became weaker, so that, when attempting to sign his daughter's admission papers, he slumped to the floor and had to be admitted to the hospital.

Information from his wife revealed that he had not been well since November 1943, when he had severe diarrhea associated with anorexia and loss of weight. One year previously he had a similar episode of weakness of the limbs, which subsided after a short nap.

In January 1944 he suffered what was termed a "stroke." His whole right lower extremity suddenly became painlessly paralyzed. He gradually recovered after a three week rest in bed. He had had nocturia, with micturition four to five times a night, all his life. Increased frequency was also present during the day. At about the age of 12 years he had had a kidney "drained," as it was supposed to have been enlarged and infected. His mother and a sister died of diabetes.

Examination of the patient shortly before admission to the hospital revealed that he was fully oriented. The exposed surfaces of the skin were deeply tanned. The heart tones were muffled. The blood pressure was 116 systolic and 80 diastolic. He was unable to sit up or hold his head erect. The fundi were normal. Examination of the cranial nerves revealed no abnormalities. There was pronounced flaccid paralysis of all four extremities, but the patient was able to move his toes. All the tendon reflexes were absent. Hyperalgesia and hyperesthesia of the plantar surfaces of both feet were present. Reexamination after his admission disclosed signs of extensive bulbar involvement. Both pupils were slightly irregular, particularly on the left. Incoordination of ocular movements was noted. The muscles of the jaw were weak, as were also the sternocleidomastoid and trapezius muscles and the muscles of the tongue. Increased tendon pain was noted at this time.

It was first believed that the patient might be suffering from periodic paralysis, and attempts were made to give him potassium chloride, which he promptly vomited. He died five hours after admission. The urine had an acid reaction and a specific gravity of 1.021; otherwise it was normal. No porphyrins were present. The blood urea nitrogen measured 210 mg., and the creatinine, 12 mg., per hundred cubic centimeters; the carbon dioxide–combining power was 25 volumes per cent; and the serum potassium, 32 mg. per hundred cubic centimeters.

*Autopsy.*—The kidneys were small and had blebs, 2 to 3 mm., on their surfaces. Microscopic examination revealed far advanced pyelonephritis.

*Microscopic Examination of Brain.*—Sections through the cerebral cortex showed widespread damage to the nerve cells. The most striking changes were of an acute nature and consisted of severe swelling and chromatolysis. Many of the nerve cells had lost almost all of their staining properties and remained as ghost cells. Interspersed among these acutely involved elements were scattered cells showing pyknosis and shrinkage and representing the remains of a more chronic and long-standing process. There was a diffuse glial increase, particularly about the vessels.

The white matter exhibited an extensive but patchy demyelination, which was most prominent about the smaller vessels, including capillaries (fig. 5*A*). In some regions this focal demyelination had resulted in the formation of small cavities, many of which were surrounded by a glial wall, of varying thickness. Glial nodules could be detected throughout the white matter.

Sections through the brain stem disclosed extensive changes within many of the cranial nerve nuclei. There was softening with complete destruction of the underlying tissue of the nuclei of the vagus nerves. The cells were swollen, fragmented and chromatolytic. Their nuclei were swollen and vacuolated. The nerve cells of the nucleus ambiguus and the descending root of the trigeminal nerve on both sides revealed primarily swelling and chromatolysis of scattered elements. The peripheral nerves appeared normal.

The spinal cord exhibited both acute and chronic changes. The anterior horn cells were swollen and rounded, having lost their processes (fig. 5 *B*). There was no vacuolation or fragmentation. The residual of chronic involvement was seen in a few small scattered, shrunken cells, the processes of which had disappeared, leaving only a small, round, distorted mass as the remnant of the injured nerve cell.

CASE 5.—A 31 year old man, with extrophy of the bladder, gave a history of recurrent attacks of motor weakness over a period of eight years. On his last admission he presented quadriparesis. The blood urea nitrogen measured 74.1 mg., and the serum potassium, 8.9 mg., per hundred cubic centimeters. He died within twenty-four hours after his last admission, of respiratory failure. Permission for autopsy was refused.

*History.*—A. L., a 31 year old truck driver, was admitted to the hospital dispensary April 18, 1944. The patient stated that one month prior to admission he had awakened in the morning to find his arms and legs paralyzed. About an hour later, however, he was able to dress and see his local physician, who thought that this disturbance might be due to his renal trouble. He had had two subsequent attacks of motor weakness. The last one occurred two weeks before admission and persisted for three days. He had had no convulsions or difficulty in breathing or swallowing.

The patient was born with extrophy of the bladder, for which he had four operations, the last being transplantation of the ureters into the colon. In 1936 he had four transient attacks of motor paralysis.

Physical examination revealed extrophy of the bladder, through which the mucosa of the bladder was visible. The penis was retracted, and the testes were descended. Neurologic examination revealed nothing abnormal. Three days later the patient was admitted to the hospital because of a sudden return of neurologic symptoms. At this time there was weakness of the left medial rectus muscle and of the sternocleidomastoid and trapezius muscles bilaterally. The deep reflexes in the upper limbs were greatly reduced or absent. The abdominal reflexes were absent. The knee jerks were hyperactive, the right being greater than the left; the ankle jerks were absent. Gordon's sign was positive on the right. The patient was able to flex slightly the fingers of both hands. The muscles of the arm and forearm were weak. In the lower limbs there appeared to be weakness only of the gastrocnemius and soleus muscles; the peroneal group was normal. Sensation was intact. Urinalysis could not be carried out because the urine was passed by rectum. The blood urea nitrogen measured 49 mg., and the creatinine, 2.1 mg., per hundred cubic centimeters, and the carbon dioxide–combining power 38 volumes per cent. The serum potassium level was 17.3 mg. per hundred cubic centimeters. A phenolsulfonphthalein test, carried out by means of enemas, yielded an excretion of 20 per cent at the end of forty-five-minutes. Roentgenographic studies of the kidneys revealed rather marked hydronephrosis of both calices and pelves. The ureters were moderately dilated. A lumbar puncture revealed nothing abnormal. The patient's condition improved while he was in the hospital, and he was discharged when the acidosis was corrected, with instructions to return at the onset of his next attack.

The patient was readmitted on July 16, 1944. Two days prior to admission he noted weakness of his left thigh. This disappeared, but the next day his right thigh was weak. On the morning of readmission he awakened almost completely paralyzed. Examination now disclosed a slight horizontal nystagmus. Conver-

gence was poor. There was weakness of the trapezius muscle bilaterally, but more pronounced on the right. The deep reflexes in the right upper limb were reduced or absent, while those in the left were uninvolved. All the abdominal reflexes were absent. The right knee jerk was increased; the left was normal. Both ankle jerks were absent. There were no pathologic toe signs. Sensation was normal. There was generalized quadriparesis, more marked on the right. The weakness of the lower extremities was more pronounced distally than proximally.

Laboratory studies revealed the blood urea nitrogen level to be 74 mg. per hundred cubic centimeters; the carbon dioxide–combining power, 16.5 volumes per cent, and the serum potassium level, 8.9 mg. per hundred cubic centimeters. When the report on the serum potassium was obtained, the patient was given 1.5 Gm. of potassium chloride intravenously. The serum potassium level one-half hour later was only 6.1 mg. per hundred cubic centimeters. The patient showed no improvement. Cardiac arrhythmia and respiratory distress developed, and he failed to recover with use of the Drinker respirator and cardiac stimuli. Administration of more potassium chloride was not beneficial, and the patient died shortly thereafter. Unfortunately, permission for autopsy was not granted.

## CLINICAL FEATURES

The symptoms of uremia can be divided roughly into two groups: those of depression of the central nervous system, e. g., apathy, muscular weakness, stupor and coma; and those of neuromuscular hyperexcitability, namely, increased tendon jerks, muscular twitchings and convulsions. The former are by far the more common and appear earlier in the illness. The patient may appear mentally and physically fatigued, tiring easily and being unable to concentrate. Dull, constant, but not severe, headaches often develop. The patient soon becomes apathetic and complains of muscular weakness and a constant feeling of drowsiness, while at the same time he may have periods of restlessness and intractable insomnia. Clouding of the sensorium, although occurring, is not the rule, many of the patients remaining well oriented until death. Speech, however, may be difficult and often unintelligible.

Symptoms of neuromuscular hyperexcitability, namely, muscular twitchings and convulsions, are frequent with uremia and often accompany the picture of lethargy, stupor or coma. The muscular twitchings are usually fibrillary and may involve large muscle groups (Oppenheimer and Fishberg [17]). The convulsions usually appear terminally and are generalized. Focal or jacksonian seizures may occur but are uncommon. Occasionally these epileptiform seizures continue even after the patient has recovered from the uremia, indicating the persistence of cortical irritation or cerebral damage.

Aside from these better known neurologic symptoms, there occur with uremia a host of less common, and often bizarre, signs, which frequently cover the entire field of neuropsychiatric symptomatology. It is when these predominate that the diagnosis is often overlooked. Most frequent are the vague, and often unusual, neurologic syndromes. Monoplegias hemiplegias, aphasias and apraxias have been reported (Fishberg,[18] Osler,[19] Saito,[16] von Monakow,[20] Boinet [21]). Of the motor symptoms, hemiplegia is the most frequent. This usually is of a flaccid type and is often ascending, producing Landry's type of paralysis. The involvement is transient, lasting hours or days and then disappearing, only to return after a variable period. Two of our patients had such episodes; in 1 the involvement implicated all limbs, resulting in quadriplegia. Hiller and Michalovici [5] described a case in which right hemiplegia with palsy of the left side of the face developed in a 26 year old man. Rothmann [22] described a case of transient amaurosis. This amaurosis may be associated with convulsions and may even remain as a permanent defect (Osler [19]). Uremic deafness can occur. Vertigo and nystagmus are infrequent symptoms (Bodansky and Bodansky [23]).

In an occasional case of uremia the mental symptoms may be the earliest, and often the predominating ones throughout the illness. The most frequent picture consists of acute confusion associated with motor unrest, incoherence and terrifying hallucinations. Occasionally there is a rapid change in mood from uncontrollable hyperactivity to depression, accompanied with hypochondriasis and delusions of persecution. Almost every form of mental illness has been described in cases of uremia, from profound melancholia to typical catalepsy with echolalia, negativism and waxy flexibility (Lemierre,[24] von

17. Oppenheimer, B. S., and Fishberg, A. M.: Hypertensive Encephalopathy, Arch. Int. Med. **41**:264-278 (Feb.) 1928.

18. Fishberg, A. M.: Hypertension and Nephritis, ed. 4, Philadelphia, Lea & Febiger, 1939.

19. Osler, W.: The Principles and Practice of Medicine, New York, D. Appleton and Company, 1892, pp. 738-740.

20. von Monakow, P.: Die zerebralen Symptome der Urämie, Schweiz. med. Wchnschr. **61**:830-833, 1931.

21. Boinet, W.: De l'hémiplégie urémique, Neurol. Centralbl. **13**:229-230, 1894.

22. Rothmann, M.: Ueber die transitorische Erblindung bei Urämie, Klin. Wchnschr. **31**:691-695, 1894.

23. Bodansky, M., and Bodansky, O.: Biochemistry of Disease, ed. 2, New York, The Macmillan Company, 1942, pp. 134-137.

24. Lemierre, M. A.: Azotémie et troubles psychiques, Bull. et mém. Soc. méd. d. hôp. de Paris **47**:1377-1382, 1923.

Hauth,[25] Menninger,[26] Bischoff,[27] Marcus,[28] Kleudgen,[29] Jacobson,[30] Grimshaw,[31] Cullerre,[32] Hagen,[33] Hoesslin[34]). Mental deterioration may occur and can be transient or permanent, depending on the severity of the cerebral injury.

Since the cerebral symptoms are not specific but merely indicate some type of involvement of the nervous system, one must always seek for any additional symptoms or signs that might help in the diagnosis. These are frequently found in the accompanying gastrointestinal symptoms and the alterations in the blood chemistry. The gastrointestinal symptoms usually consist of uremic stomatitis, a uriniferous odor of the breath, vomiting and diarrhea. The changes in the blood chemistry associated with uremia are well known and need no discussion.

### PATHOLOGIC FEATURES

A detailed histopathologic study of the central nervous system in fatal cases of uremia clearly indicates that if the illness is sufficiently prolonged, structural damage will result. The nature of these tissue changes varies primarily with the duration of the disease.

*Acute Illness.*—Gross Changes: The central nervous system may be entirely normal or may exhibit mild changes, varying from congestion to definite petechiae. Cut sections may reveal scattered punctate hemorrhages, which usually remain discrete.

Microscopic Changes: The predominant alteration in cases of acute uremia occurs within the neurons throughout the central nervous system. The earliest changes consist of pronounced swelling and partial, or even complete, chromatolysis (fig. 1 *A*). Very early these swollen cells tend to lose their staining properties, forming ghost cells (fig. 1 *B*). The cell processes often become detached, giving the cells a swollen, rounded appearance. The cell nucleus seems to be the least affected, and even in apparently severely injured elements they remain structurally uninvolved. At times the nucleus may appear mildly swollen and eccentrically placed. These neuronal changes are widely scattered and show no tendency to localize within any region. Usually the injured cells are observed scattered among apparently normal elements. In the cases of more severe and prolonged uremia, large areas of cellular devastation can be made out. Within the cerebellum, the Purkinje elements are most frequently implicated, many of them showing fragmentation of their processes, as well as an irregular loss of staining properties (fig. 2). Here, too, the nuclei appear intact. In all cases the cranial nerve nuclei are definitely involved. No particular structures appear to be selected by this process, different nuclei being involved in different cases. The cell changes are all of the acute type, producing swelling and chromatolysis.

Throughout both the gray and the white matter there appears marked vascular congestion, with some perivascular extravasation. Scattered petechiae may occasionally occur.

In those cases in which the illness lasts over five days a very early perivascular and focal demyelination results. These changes are more prominent within the white matter but do occur within the cortex and the brain stem. The perivascular myelin sheaths become swollen and occasionally fuse to produce tiny vacuolated spaces. No cellular reaction can be seen within these areas of acute perivascular alterations. Glial changes are usually not seen.

*Subacute Illness.*—When the illness lasts from a few weeks to a few months, the tissue changes are much more severe and more widespread. The neuronal involvement is prominent, particularly in the cerebral cortex and in the brain stem, where large areas of adjacent cells are injured, often producing actual areas of devastation. The nature of the injury to the nerve cells is much more variable than with the acute illness. Many of the cells still show the typical acute changes, with severe swelling and chromatolysis; however, others reveal more chronic alterations, with definite nuclear damage. Even within the acutely altered cells the pathologic process seems to be more severe, and the cell body reveals actual fragmentation, with only small fragments of cytoplasm adhering to an intact or greatly altered nucleus. Ghost cells

25. von Hauth, P.: Die psychotischen Bilder der Urämie, Allg. Ztschr. f. Psychiat. **78**:64-89, 1922.

26. Menninger, K. A.: Paranoid Psychosis with Uremia, J. Nerv. & Ment. Dis. **60**:26-34, 1924.

27. Bischoff, E.: Ueber die urämischen Psychosen, Wien. klin. Wchnschr. **11**:601-608, 1898.

28. Marcus, E.: Frühzeitige Urämie mit Tobsucht bei Scharlach, Klin. Wchnschr. **40**:584-585, 1877.

29. Kleudgen: Psychische Symptome bei chronischer Nephritis, Deutsche med. Wchnschr. **26**:445-446, 1886.

30. Jacobson, D. E.: Ueber Autointoxications-Psychosen. Allg. Ztschr. f. Psychiat. **51**:383-388, 1895.

31. Grimshaw, T. W.: A Case Presenting Cataleptic Symptoms, Dublin J. Med. **59**:349-355, 1875.

32. Cullerre, A.: Délire aigu et urémie, Arch. de neurol. **12**:449-452, 1901.

33. Hagen, H.: Ueber Nierenkrankheiten als Ursachen von Geisteskrankheit, Allg. Ztschr. f. Psychiat. **38**:1-34, 1882.

34. Hoesslin, R.: Ueber psychische Erkrankungen bei chronischer Nephritis, München. med. Wchnschr. **36**:717-718, 1889.

are numerous. Scattered among these swollen and fragmented elements are many nerve cells that have undergone a chronic change (fig. 6). Both the cell body and the nucleus appear pyknotic; the Nissl granules are coarse and clumped, and the cell processes are retracted, narrowed and blunt. This admixture of acute and chronic damage to nerve cells is prominent within the cranial nerve nuclei, where occasionally all the components of a nuclear group show some involvement, without leaving a single structurally intact cell.

The demyelination in this stage of the disease is also much more extensive and, although

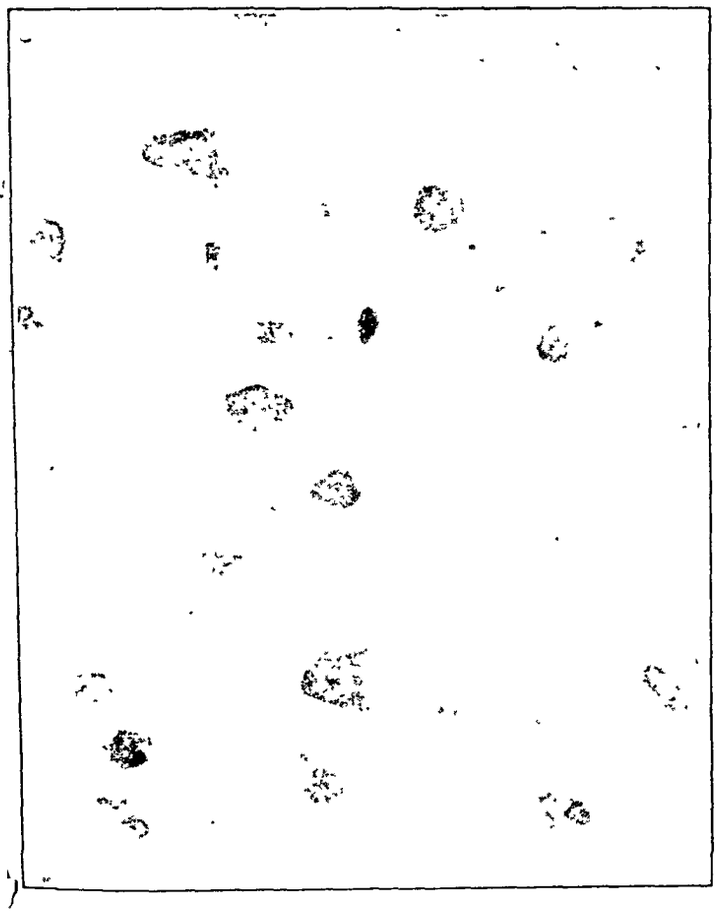


Fig. 6 (case 3).—Subacute neuronal changes within the cortex. The cell body has undergone some fragmentation, leaving only cytoplasmic fragments adhering to the nucleus. Nissl stain.

appearing within the cortex, is much more prominent within the white matter. This demyelination is both focal and perivascular and extends for considerable distances into the adjacent tissues (figs. 4 and 5 *A*). In many of these perivascular areas the demyelination is almost complete and is partially replaced by fat granule cells (fig. 3). In addition to this demyelination, there occur scattered foci of necrosis, often filled with necrotic brain tissue and fat granule cells. In an occasional field these necrotic areas have been fairly well cleared of injured brain tissue, producing tiny cavity formations. The glia shows a mild diffuse increase. The greatest tendency for glial reaction appears to be in the vicinity of the necrotic foci. Vascular congestion is not conspicuous in this stage of the illness, although scattered ball hemorrhages are frequently encountered.

*Chronic Illness.*—When the illness lasts many months or years, the predominant tissue change tends to be parenchymal rather than neuronal. The nerve cells now reveal predominantly chronic alterations, consisting of pyknosis and shrinkage. Many of the cells appear as tiny dark masses, within which none of the cell structures can be identified. Many neurons have entirely disappeared, leaving a considerable reduction of the normal elements. This complete disappearance of cells is most noticeable in the cerebellum and the brain stem. Frequently acute changes accompany the more chronic ones, indicating continuation of the pathologic process.

The demyelination and tissue necrosis are striking in this stage of the illness. Both are associated with fat granule cell reaction. In many areas these foci of tissue injury have resulted in the formation of small cavities, many of which contain a few scavenger cells and are surrounded by a glial wall, of varying thickness. Glial nodules occasionally are present throughout the white matter.

Vascular congestion and petechiae are usually absent. The small vessels, in spite of the use of special staining technics, reveal no consistent changes within their walls. In a few scattered vessels the walls reveal patchy impairment of their staining properties.

## COMMENT

The question might be raised as to whether the lesions described were due entirely to the uremic intoxication, since many patients with uremia do have a pathologic condition of the kidneys associated with circulatory abnormalities. In order to reduce to a minimum such complicating vascular alterations or changes due to age, an attempt was made to select for study primarily cases from the younger age group, in which the vascular abnormalities would be less likely to occur. Moreover, 4 of our patients suffered from extrarenal uremia, with no indication of a pathologic condition of the kidneys. In none of the reported cases was there any significant pathologic evidence of circulatory disturbance. This absence of detectable cerebrovascular lesion, the constancy of the histologic changes and their increased severity with the more chronic disease and, finally, the simi-

larity of the observations in both the renal and the extrarenal forms of uremia forced us to conclude that these changes were probably produced by the uremic intoxication.

The possible cause of such cerebral complications in cases of uremia still remains a moot question in spite of extensive investigations. The experimental data thus far accumulated would indicate that the uremia syndrome is the result of a disturbance of electrolytes, an increase in nitrogenous metabolites within the blood or the evolution of some toxin hitherto unrecognized. The last view finds some support from the interesting investigations of Foster.[35] Basing his work on Herter's observation that the blood of uremic patients was more toxic to dogs than the blood of normal persons, Foster isolated a crystalline substance from uremic blood which killed guinea pigs when injected intraperitoneally. Some animals died of convulsions in fifteen minutes; others died less rapidly and prior to death had paresis or paralysis of the hindlegs. Foster's work, although extremely significant, has, unfortunately, not as yet been corroborated.

The work of Harrison and Mason[36] and Mason and associates[37] would indicate that in uremia the brain is subjected to two antagonistic influences, one stimulating, the other depressing. According to these investigators, the increased neuromuscular irritability is apparently due to more than a deficit of ionized calcium, as injections of a suitable calcium salt will not always alleviate the symptoms. De Wesselow[38] and Harrison and Mason[36] found no connection between the diminution of serum calcium and the generalized convulsions. Becher[39] and de Wesselow[38] placed a greater prognostic value on the rise in serum phosphates than on the deficit of calcium.

The depression in functions of the nervous system associated with uremia has been suspected by some to be due to a rise in blood phenols (Dickes,[40] Becher[39b] and Mason and associates[37]). These authors did not agree as to whether the phenols must be free or can be combined. Certainly, chronic phenol poisoning produces a clinical picture resembling that in some cases of uremia.

More recently, a great deal of interest has been centered on the significance of altered potassium levels of the blood of uremic patients. The recent work of Brown, Currens and Marchand[41] seems to indicate that too high a level of blood potassium is as dangerous as too low a level. Cardiac arrest may develop from either, as cases 5 and 6 in our series indicate. The changes in the electrocardiogram may be helpful in cases of this type.

## SUMMARY AND CONCLUSIONS

1. Uremia, although usually treated by the internist, occasionally results in symptoms that may cover the entire field of neuropsychiatric symptomatology.

2. The most common symptoms referable to the nervous system are convulsions and coma, but in isolated cases unusual syndromes, such as monoplegias, hemiplegias, aphasias and apraxias, or even mental symptoms of almost every type, may be present.

3. The central nervous system in cases of uremia reveals widespread tissue changes involving both the nerve cells and the parenchymal elements. In the acute illness the predominant alteration occurs within the cortical neurons, which reveal an acute change in the nerve cells. In the more chronic illness the most striking changes are parenchymal rather than neuronal and consist of focal and perivascular areas of demyelination and necrosis. The neurons show both acute and chronic changes in the more chronic illness.

35. Foster, N. B.: The Isolation of a Toxic Substance from the Blood of Uremic Patients, Tr. A. Am. Physicians **30**:305-307, 1915.

36. Harrison, T. R., and Mason, M. T.: The Pathogenesis of the Uremic Syndrome, Medicine **16**:1-44, 1937.

37. Mason, M. F.; Resnik, H.; Minot, A. S.; Rainey, J.; Pilcher, C., and Harrison, T. R.: Mechanism of Experimental Uremia, Arch. Int. Med. **60**:312-336 (Aug.) 1937.

38. de Wesselow, O. L. V.: On Phosphorus and Calcium of the Blood in Renal Disease, Quart. J. Med. **16**:341-362, 1923.

39. Becher, E.: (*a*) Studien über die Pathogenese der echten Urämie, insbesondere über die Bedeutung der retinierten Phenole und anderer Darmfäulnisprodukte, Zentralbl. f. inn. med. **46**:369-383, 1925; (*b*) Pathogenese, Symptomatologie, und Therapie der Urämie, Ergebn. d. ges. Med. **18**:51, 1933.

40. Dickes, R.: Relation Between the Symptoms of Uremia and the Blood Levels of Phenols, Arch. Int. Med. **69**:446-455 (March) 1942.

41. Brown, M. R.; Currens, J. H., and Marchand, J. F.: Muscular Paralysis and Electrocardiographic Abnormalities Resulting from Potassium Loss in Chronic Nephritis, J. A. M. A. **124**:545-549 (Feb. 26) 1944.

# ELECTROENCEPHALOGRAM OF DOGS WITH EXPERIMENTAL SPACE-OCCUPYING INTRACRANIAL LESIONS

GEORGE ULETT, M.D., PH.D.
PORTLAND, ORE.

The controlled reproduction in laboratory animals of pathologic conditions which produce alteration in the electroencephalogram is one approach toward an understanding of abnormal brain waves. Foerster and Altenburger [1] have shown that tumor tissue itself is apparently electrically inert and that the changes observed electroencephalographically with such lesions are recorded from tissue surrounding the tumor. Hence it has seemed logical to use a noncellular material to simulate the space-occupying lesions observed clinically. The procedure of introducing foreign bodies in the brain is not new,[2] and the histologic changes from foreign bodies in the brain have been reported by several workers.[3] Experimental subdural and extradural hematomas in rabbits have been reported by Glaser and Sjaardema [4] to cause alteration in the electroencephalogram characterized by the disappearance of normal frequencies and the appearance of slow waves mixed with rapid activity.

An understanding of the alterations in the anatomic and physiologic state essential for the production of abnormal slow waves is one of the problems suggested by clinical electroencephalography. The term "delta wave" was coined by Walter [5] to describe such abnormally slow potentials seen in the electroencephalogram in cases of focal intracranial lesions. Pressure on cortical layers,[6] lowered excitability of cortical neurons from intoxication or circulatory embarrassment [7] and disturbance of pathways in the white matter [8] have each been advanced as a possible causative mechanism for these potentials.

## METHOD

Records were taken with a Grass four channel, ink-writing electroencephalograph on 25 adult dogs that were trained to lie quietly in an animal holder, the muzzle of which prevented movements of the head. By use of steel needle electrodes [9] placed into the skull through the procainized scalp, it was possible to obtain records free from artefact. With anesthesia induced with pentobarbital sodium, a hollow threaded, stainless steel plug with a self-sealing rubber diaphragm (fig. 1 *A*) was screwed into a tapped hole through the parietal area of the skull of each dog without injury to the dura. Two weeks after operation, when the scalp had completely healed over the plug, electroencephalograms were taken and were compared with control records taken before operation to insure that there had been no damage to the underlying brain. A sterile mixture of white wax U. S. P. softened with iodochlorol (a radiopaque, chloriodized peanut oil) or liquid petrolatum was injected into the brain through a 20 gage hypodermic needle thrust through the surgically prepared, anesthetized scalp and the rubber diaphragm of the hollow metal plug (fig. 1 *B*). The injection was accomplished by means of a metal syringe, whose plunger was activated in "grease gun" fashion by a threaded turnscrew. After the injection, electroencephalograms were taken at frequent intervals, until the experiment was terminated with a bilateral craniotomy performed with the dog

From the Department of Anatomy, University of Oregon Medical School.

Dr. Robert Dow directed this study, and Dr. Knox Finley gave guidance in neuropathologic interpretation.

This study was aided by a grant from the Committee on Scientific Research of the American Medical Association.

1. Foerster, O., and Altenburger, H.: Elektrobiologische Vorgänge an der menschlichen Hirnrinde, Deutsche Ztschr. f. Nervenh. **135**:277, 1935.

2. von Schultén, M. W.: Untersuchungen über den Hirndruck, mit besonderer Rücksicht auf seine Einwirkung auf die Circulations-Verhältnisse des Auges, Arch. f. klin. Chir. **32**:947, 1885.

3. Tschistowitsch, T.: Ueber die Heilung aseptischer traumatischer Gehirnverletzungen, Beitr. z. path. Anat. u. z. allg. Path. **23**:321, 1898. Hassin, G. B.: Reacting Cells in the Brain in the Presence of a Foreign Body, Arch. Neurol. & Psychiat. **36**:231 (Aug.) 1936. Ward, J. W., and Clark, S. L.: The Production of Artificial Tumors in the Brains of Cats, J. Lab. & Clin. Med. **26**: 1778, 1941.

4. Glaser, M. A., and Sjaardema, H.: Electro-Encephalographic Diagnosis of Extradural and Subdural Hemorrhage, Proc. Soc. Exper. Biol. & Med. **47**: 138, 1941.

5. Walter, W. G.: The Location of Cerebral Tumours by Electroencephalography, Lancet **2**:305, 1936.

6. Gibbs, F. A., and Gibbs, E. L.: Atlas of Electroencephalography, Cambridge, Mass., Lew A. Cummings Company, 1941.

7. Beritoff, J., in Transactions of the Physiological Institute of the Georgian Academy of Sciences, Georgian SSR, 1943.

8. Stewart, W. A.: Electroencephalographic Changes Associated with Different Forms of Experimentally Produced Increased Intracranial Pressure, Bull. Johns Hopkins Hosp. **69**:240, 1941. Williams, D.: The Abnormal Cortical Potentials Associated with High Intracranial Pressure, Brain **62**:321, 1939.

9. Hoagland, H.: A Simple Method for Recording Electrocorticograms in Animals Without Opening the Skull, Science **92**:537, 1940.

under ether anesthesia. At this time 1 mm., cotton wick core, steel tube electrodes were placed, four on each side of the exposed cortex. After liberal use of procaine hydrochloride in the scalp, the ether anesthesia was stopped, and electrocorticograms were taken over periods of up to three hours. The animal was then killed with an overdose of pentobarbital and the brain removed, fixed in 95 per cent alcohol or in solution of formaldehyde U. S. P. diluted 1 : 10, embedded in pyroxylin or paraffin, cut at 20 microns and the sections stained with hematoxylin and eosin and with the methods of Nissl and Weigert.

## RESULTS

*Brain Potentials of the Unanesthetized Dog.*—The electroencephalograms recorded from 40 normal unanesthetized dogs in this laboratory have been characterized by a dominant frequency of from 20 to 30 cycles per second. Occasional waves at lower frequencies were seen, especially in younger dogs. Electrocorticograms were obtained from the exposed brain in 16 dogs with the scalp under local anesthesia. The electrocorticograms resembled the electroencephalograms in all ways except for an increased voltage. In animal recordings one must be constantly on guard for artefacts due to muscle potentials and to respiratory and other movements of the animal. Liberal use of procaine in the scalp, training and close observation of the animal and rigid fixation of the head resulted in records which were relatively free from artefacts.

*Dogs with Intracerebral Lesions.*—Successful intracerebral injections of white-wax mixture were accomplished in 20 dogs, and electroencephalographic tracings were taken from one minute to four months after the injection. Except in 3 dogs in which there occurred a slight diminution of amplitude of the spontaneous activity on the side of operation the surgical placement of the metal injector caused no change in the record. Records were taken in 3 instances within ten minutes of the time of injection, 2 of these being taken sixty seconds after the injection. In 24 instances records were made on the first or second day; in 11, on the third and fourth days; in 8, on the fifth and sixth days, and in 8, after the sixth day. The electroencephalogram was recorded from 1 animal four months after the injection. Figure 2*B* summarizes the findings in the records of 19 dogs studied in this manner. One dog was excluded from this tabulation because of the presence of infection. The indexes were obtained by counting the waves in a thirty second, artefact-free sample selected as being representative, in each case, of a much longer recording.

The most noticeable alteration in the recorded electroencephalogram was the appearance of large delta waves (1 to 3 cycles per second at 20 to 60 microvolts) and the disappearance of the normal fast frequencies. This change was seen as soon as thirty seconds after the injection and was very noticeable in records taken on the first and second days after the lesion was made. Following this there was a gradual return toward the normal record, with a decrease in amplitude of all abnormal activity and the progressive disappearance of the delta waves, affecting the slowest waves first. After the seventh day the record appeared fairly normal to casual inspection, and in dogs seen from two weeks to four months after the injection the electroencephalogram could not be told from a preinjection record. Figure 2*A* shows the typical sequence of electroencephalographic alterations as demonstrated by a dog in which 1.5 cc. of white wax–iodochlorol mixture

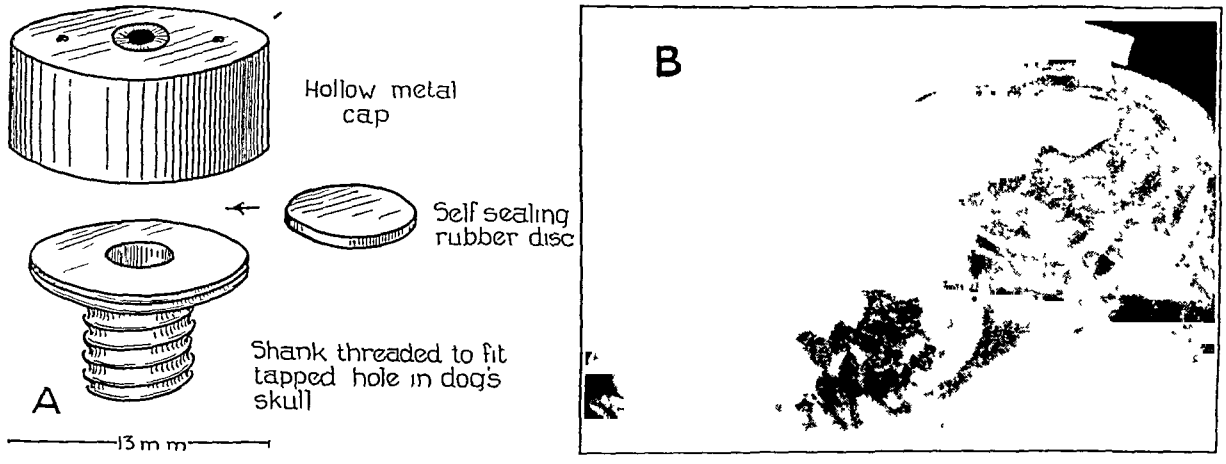
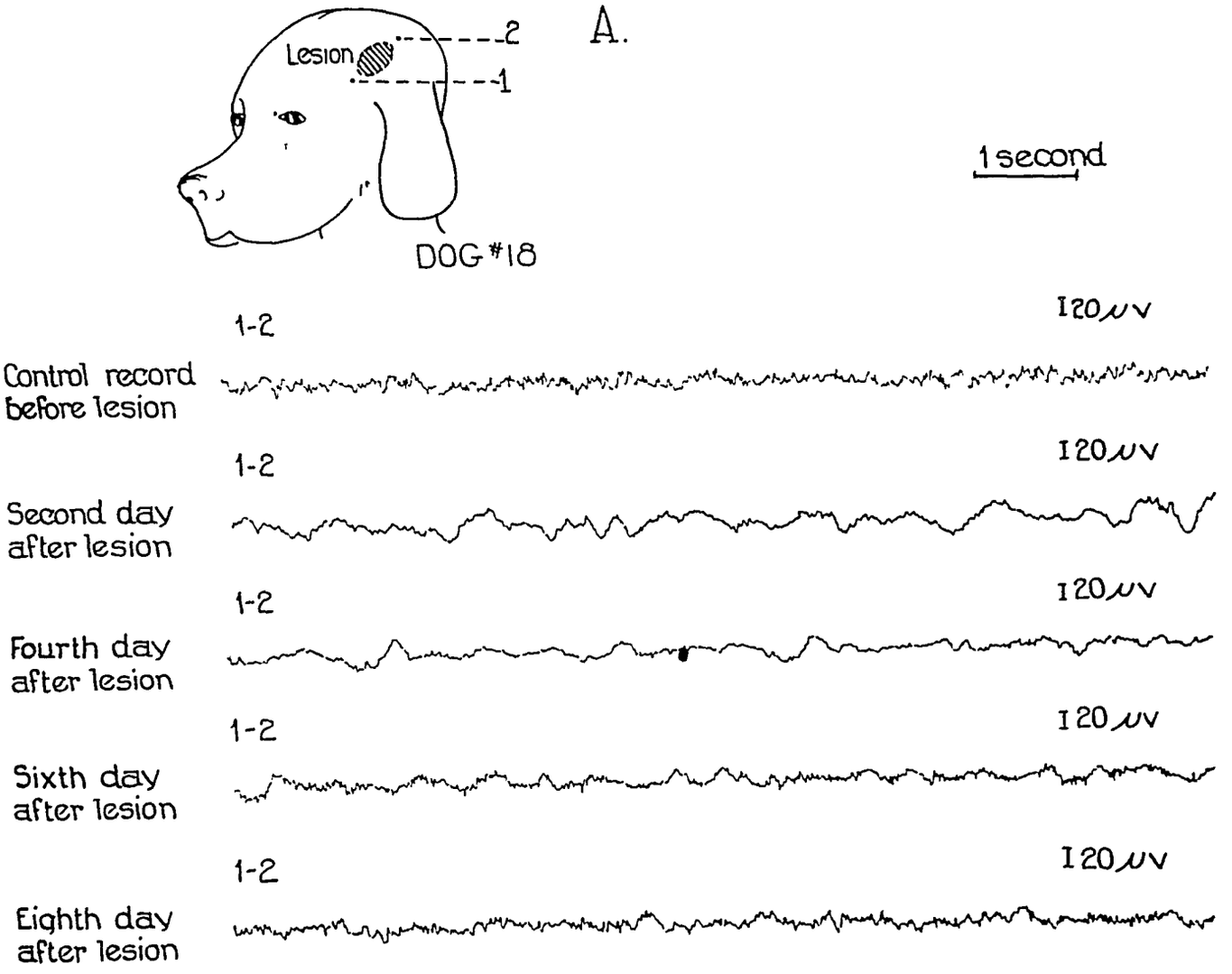



Fig. 1.—*A*, hollow, stainless steel plug designed to permit intracerebral insertion of space-occupying lesions. *B*, roentgenogram of dog's head, showing steel plug in position in the skull and intracerebral radiopaque mass which has been injected through it.

was injected just below the cortex. Bipolar recording from six electrodes placed linearly across the involved hemisphere permitted localization of the lesion by a focus of out of phase delta activity similar to the foci seen in electroencephalographic localization studies on human patients. In figure 3 *B* the type of electroencephalographic disturbance produced experimentally in the dog by the intracerebral injection of wax is compared with a similar disturbance which may be seen with intracranial neoplasm in the human subject.

In the early experiments some discrepancies in the sequence of electroencephalographic



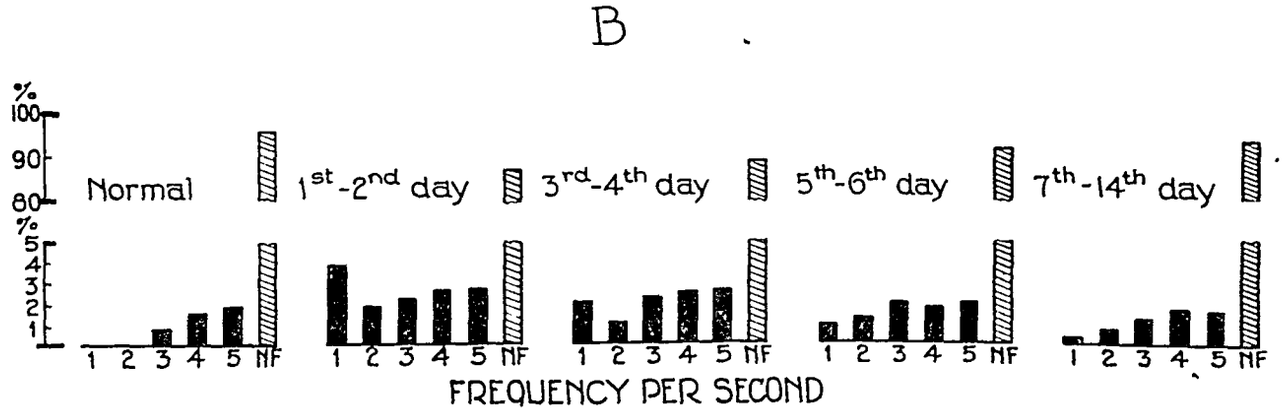




Fig. 2.—*A,* electroencephalogram as recorded from skull electrodes in a dog under local anesthesia with 1.5 cc. of wax mixture placed intracerebrally. The control record was taken just before, other records at intervals after, the injection. *B,* brain wave frequency spectrums determined by counting the waves in sample strips of electroencephalograms from 19 dogs with intracerebral lesions. The normal spectrum was determined from records taken before injection; the other spectrums, from records taken at intervals after injection of the intracerebral wax masses. The cross-hatched bar, *NF* (normal fast), represents all frequencies above 5 cycles per second, which make up the greater number of waves in the electroencephalogram of the dog when awake. (Note that the percentage scale is nonlinear.)

changes were observed. Later observations on the placement of electrodes through the scalp revealed that early occasional failure to record existing abnormalities could be explained by slight changes in electrode placement. A shift of electrodes, a distance as small as 5 mm., could mean the difference between a relatively normal and an abnormal record.

The initial injection of the wax–iodochlorol mixture used in the 20 dogs varied from 1 to 2 cc. in amount. Both white wax–iodochlorol and white wax–liquid petrolatum mixtures were used, in order to ascertain the chemical effect of iodochlorol on the electroencephalogram. Similar results were obtained with the two mixtures. Three dogs in the series were given additional injections after the original disturbance of the electroencephalogram had disappeared. In 1 of these animals the total intracerebral mass of 5 cc. caused death within twelve hours. In the other 2 dogs the additional wax again produced slow abnormal potentials in the electroencephalogram. In the infected dog the wax mass lay virtually within a brain abscess. The electroencephalogram of this animal was characterized by high voltage delta waves, which continued unabated until the death of the animal, four days later. Encroachment of this wax mass on the motor area occurred in 1 dog. In this animal there developed typical jacksonian convulsions, first observed twenty-four hours after the injection. These attacks were of five to forty seconds' duration and occurred every twenty to thirty minutes until the dog was killed, after six hours of observation. Records taken during this period showed rapid high voltage, spiking activity of the type that has been described in the electroencephalogram of patients during convulsive seizures. This activity was more marked on the side of the lesion. Postseizure recordings showed intermittent brief periods of cortical inactivity, and the interseizure records revealed delta activity, most pronounced on the side of the lesion.

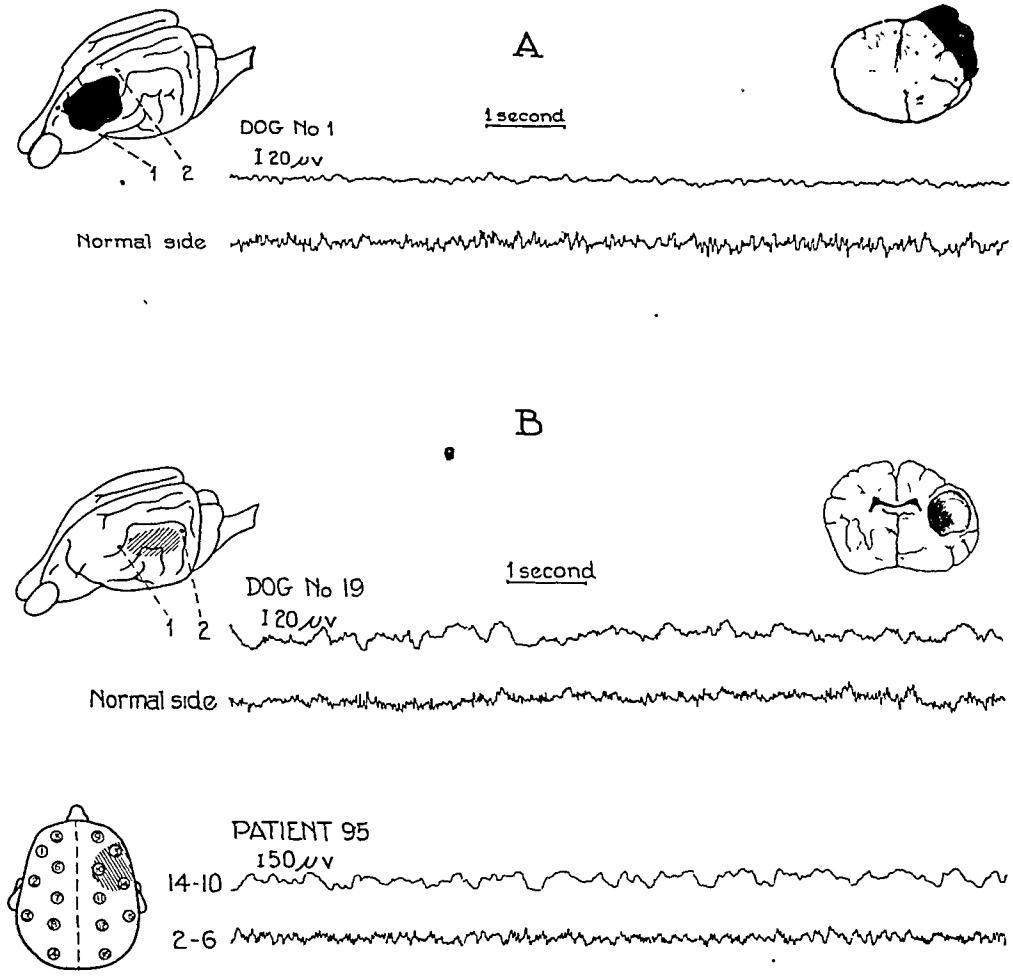



Fig. 3.—Electroencephalograms recorded simultaneously from the side of the lesion and from a homologous area on the normal side in (*A*) a dog with an extradural space-occupying lesion, and (*B*) a dog with an intracerebral space-occupying lesion and a patient with cerebral astrocytoma.

In dogs with intracerebral lesions the transient focal changes could still be detected in the electrocorticogram at a time when the record from electrodes in the skull revealed an apparently normal electroencephalogram. Leads from the

skull are much less efficient in detecting abnormal cerebral activity, as produced here in dogs, than are leads placed directly on the surface of the brain. Figure 4 A shows the striking difference between records obtained from the skull and those cerebral injections of wax. It was found that cortical recordings at points progressively removed from the lesion produced records which more nearly resembled the normal control record from the opposite side (fig. 4 *B*). It was found,

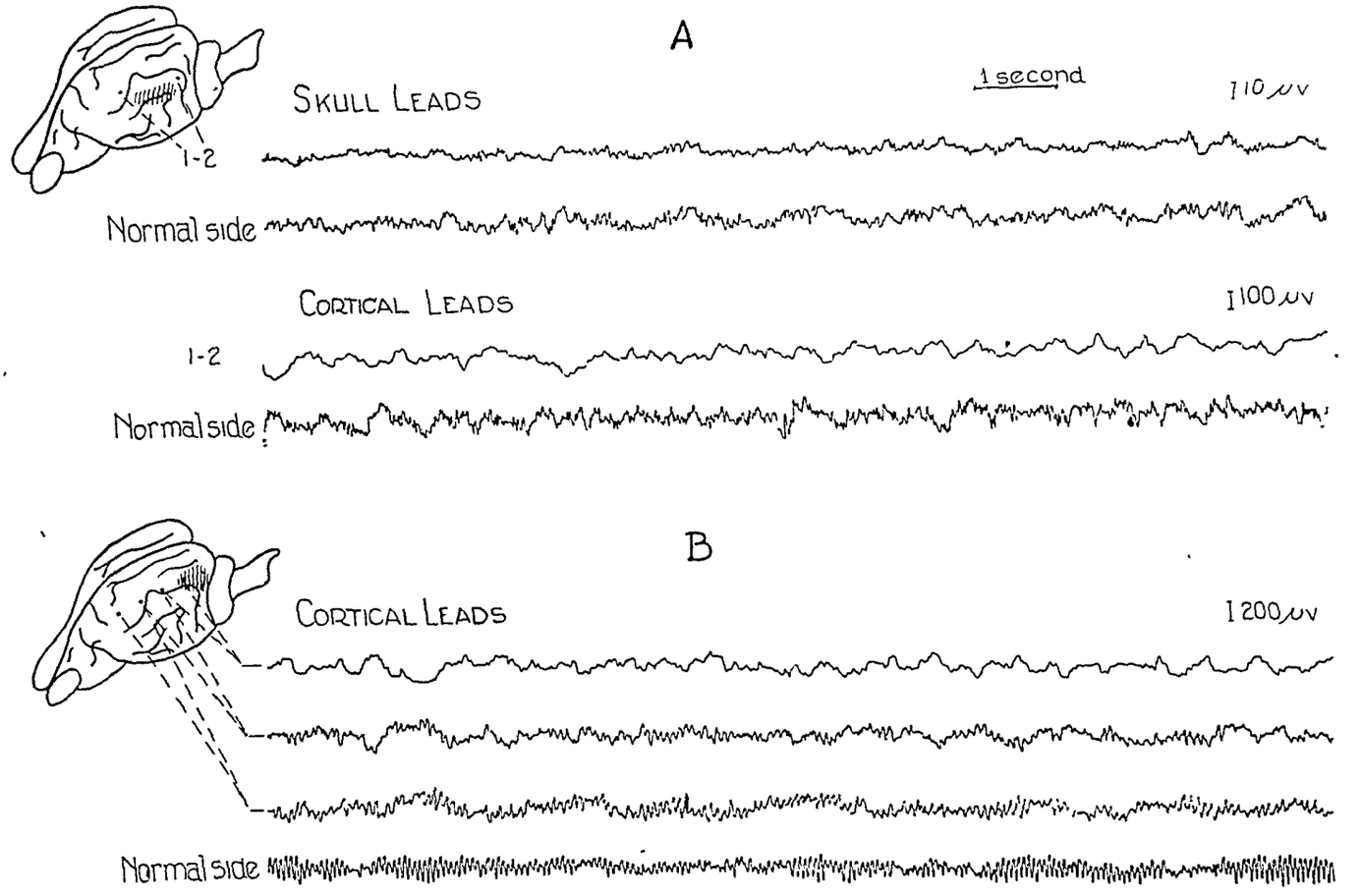



Fig. 4.—*A*, comparison of an electroencephalogram recorded from skull electrodes and records taken by cortical leading from an unanesthetized waking dog ten days after the placement of an intracerebral lesion, and at a time when the focal abnormality as seen with skull recording had nearly disappeared. *B*, brain potentials as recorded from the cortex of a dog under local anesthesia twelve days after production of an intracerebral lesion. The first three strips were recorded from successive pairs of electrodes on the side of the lesion. The fourth strip is from an area on the normal side, homologous to that from which the first strip was recorded.

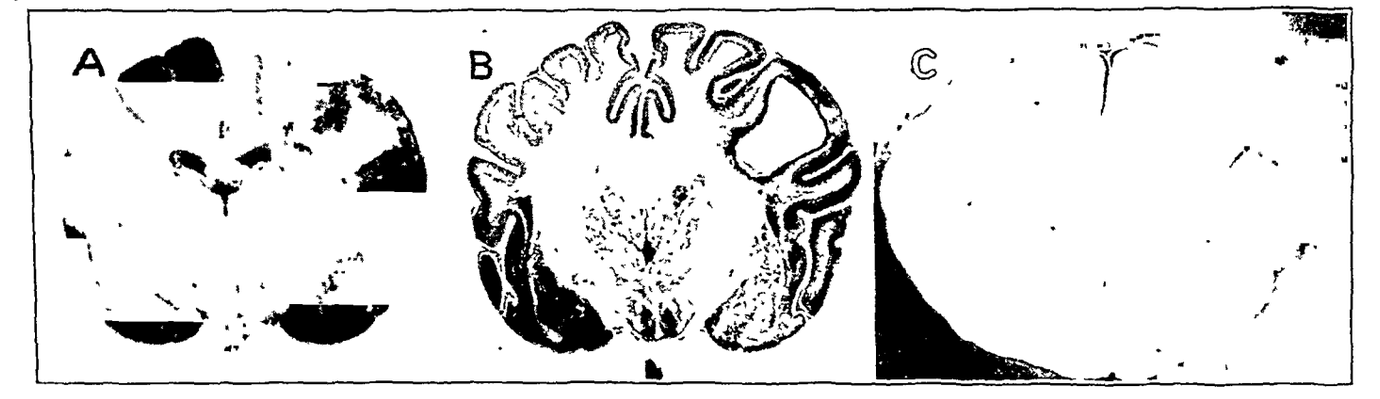



Fig. 5.—*A*, section through the brain of a dog with an intracerebral lesion; *B*, Nissl preparation of the same section; *C*, section through the brain of a dog with an extradural lesion.

from the cortex ten days after injection. Cortical leads on tissue immediately adjacent to a point of injection exhibited alteration in the electrocorticogram (slow potentials and decreased amplitude of normal waves) one minute after intra- however, that definitely abnormal records could be obtained at a distance from the injected mass with the electrode over brain tissue that appeared normal to both gross and microscopic inspection.

Histologic preparations of the brains of dogs with intracerebral lesions (fig. 5 *A* and *B*) showed initially swelling of the brain tissue and a reacting zone of capillary proliferation, with perivascular appearance of polymorphonuclear leukocytes and lymphocytes. On the fourth day the ring of tissue immediately adjacent to the lesion showed increasing density on low power examination. This ring was composed of gitter cells and of proliferating fibroblasts, the latter originating apparently from the newly formed capillaries. The gitter cell reaction reached its height on the sixth to the eighth day. After the eighth day the gitter cells decreased in number, until by the fourth month none were to be found. Concomitant with this change the bipolar fibroblasts became more prevalent, arranged themselves in rows parallel with the borders of the lesion and by the fourth month were seen to have formed a dense, fibrous capsule completely surrounding the wax mass.

Changes in neurons were visible only where the lesion bordered directly on the gray matter. In these lesions chromatolysis, vacuolation of cells and distortion of architectonic layering were present but not common. Such changes were seen first on the second day but were equally numerous on the sixth day, at a time when the abnormality in the electroencephalogram as recorded from electrodes in the skull had almost disappeared. It was not possible to determine if these changes in the ganglion cells were reversible, as the number of damaged ganglion cells was small and evidence of dropping out of such cells at later stages of the process could not be detected. Some proliferation and swelling of astrocytes and increase in the number of microglia nuclei were seen in the neighboring gray matter, particularly after the third day. Interfascicular oligodendrocytes seemed most numerous about the lesion on the second to the fourth day. Some degeneration of myelin was seen by the fourth day in Weigert sections. The spread of demyelination along bordering fiber tracts was, however, more in evidence by the second week.

*Dogs with Subdural and Extradural Lesions.*—In 5 animals subdural or extradural lesions were produced incidentally to the study of intracranial lesions. Although the series is small, the findings are of interest and deserve a more thorough investigation. In these animals from 1 to 3.5 cc. of wax mixture was injected subdurally (2 dogs) or extradurally (3 dogs). Records were taken on these animals from thirty seconds to two days after the injection. With this type of lesion slow delta waves were not seen; instead there was a selective loss of the normal frequencies, fast and slow. In all cases the record from the site of the lesion appeared almost completely flat at an amplification that had previously been adequate for normal recording. The electroencephalograms from the side opposite the lesion were used as controls and showed no changes from the preinjection records. The aforedescribed alterations in the electroencephalogram were seen at all times, from thirty seconds after injection until the animals were killed, after the second day.

The possibility exists that simply the presence of an electrically inactive mass between the electrode and the cortical tissue can serve to decrease the amplitude of the recorded electroencephalogram. This, however, was not an important factor, because reduction of amplitude was observed with the electrodes placed on the cortex after the mass had been removed. Figure 3 *A* shows the electroencephalogram as recorded from a dog with such an extradural lesion.

Sections were made from these brains after the second day of the lesion. Grossly the section showed indentation and deformity of the cerebral cortex (fig. 5 *C*). Microscopic examination showed neuronal changes, including chromatolysis, swelling and vacuolation of cells on the side of the lesion. No demyelination was demonstrable in Weigert preparations, and no glial or mesenchymal reaction was seen in the brain substance. Although all histologic sections were from animals killed two days after the lesion was introduced, it seems reasonable to believe that changes recorded in the electroencephalogram as soon as one minute after the injection were not dependent on such histologically demonstrable alterations in brain tissue.

*Effect of Focal Abnormality on the Brain Potentials of Sleep and Pentobarbital Anesthesia.*—The electroencephalograms of unanesthetized dogs during sleep have been recorded in this laboratory incidentally to the investigation of other problems. Such records are characterized by the appearance of waves of somewhat higher amplitude and slower than normal frequencies (3 to 5 cycles per second) and by the disappearance of much of the normal fast activity. Two dogs in the present study fell asleep during the recording of the electroencephalogram. One of these animals had had wax injected intracerebrally thirteen days previously; the other had an extradural injection of wax mass two days before the record was taken. In both instances the characteristic sleep pattern was seen only on the normal side.

In both dogs the disturbance could be caused to disappear by awakening the animal, only to have it reappear again with the advent of sleep (fig. 6*A*).

The record of the dog under pentobarbital anesthesia characteristically consists of high voltage, irregular groups of waves of 5 to 10 cycles per second occurring against a background of waves of 3 to 12 cycles per second. Similar activity has been described in the cat.[10] For 7 dogs records were made with pentobarbital anesthesia from two to twelve days after intracerebral injection of wax mixture. In 2 cases the record was from scalp leads, and in 5 from the exposed cortex, as a terminal procedure in the experiment. A difference was observed between the normal side and the side of the lesion in all the dogs anesthetized with pentobarbital. The differences, however, were less marked than in the unanesthetized dogs. Spontaneous bursts of activity during pentobarbital anesthesia were of considerably less amplitude on the side of the lesion in some animals (fig. 6*B*).

## COMMENT

The mechanism of the production of abnormally slow brain potentials in cases of space-occupying intracranial lesions is not known. However, the presence of occipital and posterior parietal delta waves in cases of tumors lying entirely within the posterior fossa [11] points to some mechanism for production of slow waves other than the direct effect of neoplastic cellular metabolism. Furthermore, it has been shown by Murphy and

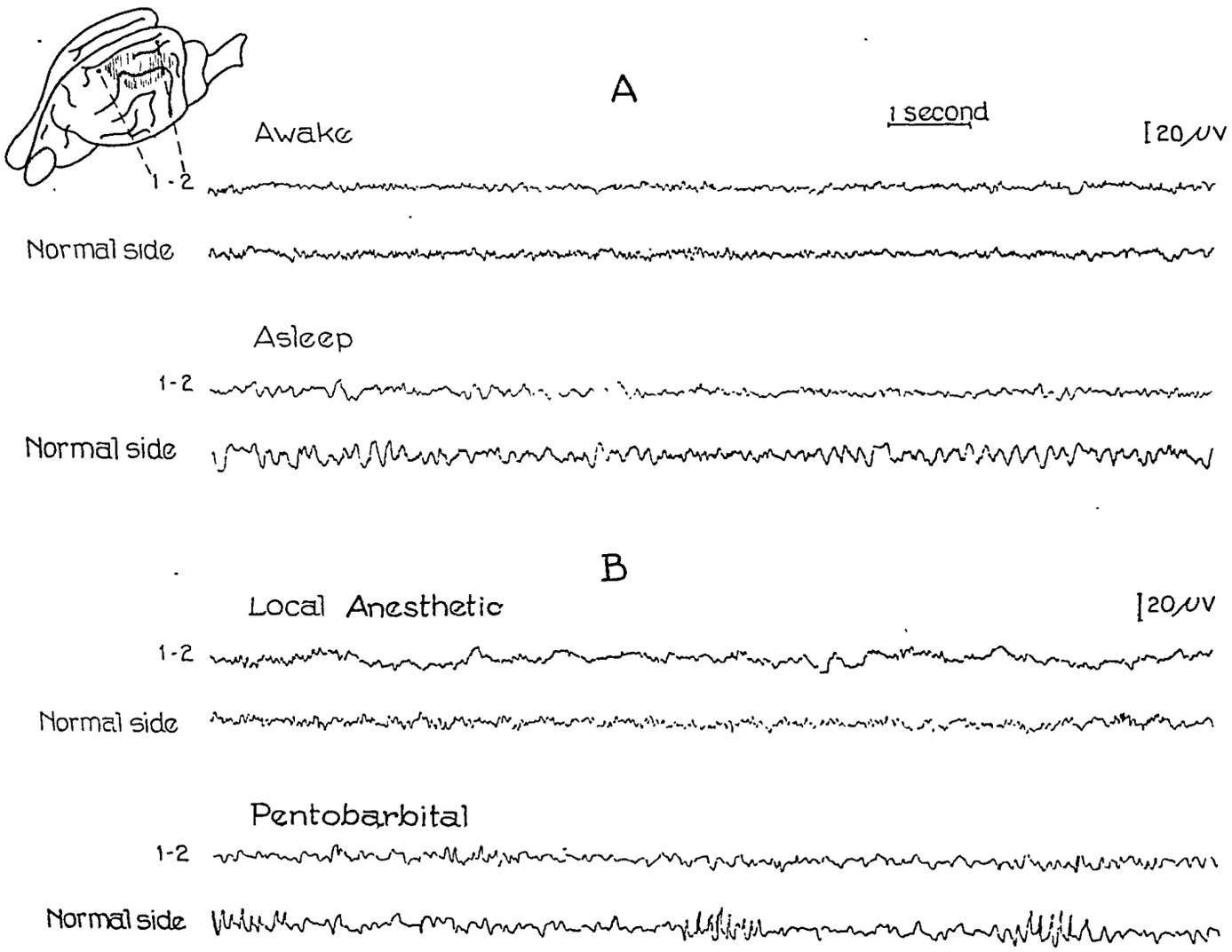



Fig. 6.—Electroencephalograms from skull electrodes in dogs with intracerebral lesions and with procainized scalp. (*A*) The upper records were taken with the animal awake. The lower strips, taken during sleep, demonstrate the relative absence of slow waves on the side of the lesion. (*B*) The upper record was taken when the dog was awake. The lower strips, taken after the intravenous injection of 3 cc. (200 mg.) of veterinary pentobarbital sodium (15 pound [6.8 Kg.] dog), show relative absence of spindles characteristic of pentobarbital anesthesia in records taken on the side of the lesion.

10. Morison, R. S.; Finley, K. H., and Lothrop, G. N.: Spontaneous Electrical Activity of the Thalamus and Other Forebrain Structures, J. Neurophysiol. **6**:243, 1943.

11. Smith, J. R.; Walter, C. W. P., and Laidlaw, R. W.: The Electroencephalogram in Cases of Neoplasms of the Posterior Fossa, Arch. Neurol. & Psychiat. **43**:472 (March) 1940.

Dusser de Barenne [12] that products of tissue destroyed by thermocoagulation have the effect of lowering the $p_H$ and bring about a reduction of cortical activity. The present experiments illustrate well that the presence of inert intracerebral masses results in the appearance of slow waves from adjacent cerebral tissue. In this work the immediate appearance of abnormal potentials makes it seem reasonable to conclude that delta waves can occur apart from evident inflammation or edema as demonstrated by routine histologic study.

Although mechanical pressure from a foreign body lying within the white matter appears to be an adequate stimulus for slow activity, the abnormal potentials so produced soon tend to disappear provided that the lesion remains of fixed dimensions. Further increase of pressure at a later date (i. e., after the dog's electroencephalogram had returned to normal) reactivated the sequence of electroencephalographic alteration. This observation points to the necessity for continued activity (growth, irritation, etc.) of the causative agent as essential for the maintenance of abnormal electroencephalographic activity.

Walter [5] and other workers [6] have suggested that injury to the overlying cortex is essential for focal electroencephalographic abnormalities. Were this the case, it would seem that pressure on the cortical layers from above would be more likely to produce slow waves than pressure from a mass lying almost entirely within the white matter and producing pressure on the cortex only indirectly. In the experience of my associates and myself, however, this has not been the case, and pressure on the cortex from subdural and extradural experimental lesions and in certain clinical cases of meningioma has not produced high voltage slow waves. This is in contrast to the prominent delta activity seen by us in cases of cerebral astrocytoma and brain abscess and in experimental lesions in dogs when the lesion was placed within the white matter of the brain (fig. 3 *B*).

In the light of Kennard's [13] work, which showed that lesions in basal forebrain structures were productive of abnormal slow waves in the electroencephalogram, one must consider the possibility that delta waves seen in our experiments might have arisen from pressure on such structures. Examination of histologic preparations from the brains of our experimental animals, however, showed that such basal structures were not directly involved by these lesions.

It is seen from our experiments that surface compression eliminates cortical activity. It is our opinion that certain low voltage slow waves (4 to 8 cycles per second) without superimposed faster frequencies occasionally seen at the periphery of our subdural and extradural lesions may have been the result of sparing of the deep cortical layers, which presumably would be less affected near the borders of a surface compression. This opinion is in keeping with the observation that thermocoagulation limited to the outer cortical layers left a low voltage slow potential wave in the electrocorticogram.[14] Although these slow waves have been termed "delta-like,"[15] it seems to us that they may well be the low voltage slow component of the normal electroencephalogram which, in the intact cortex, combines with faster frequencies, presumably coming from more superficial layers of the cortex,[16] to give the full spectrum of the normal electroencephalogram. Such slow waves can be differentiated by their low amplitude and short wavelength from the high voltage delta discharge seen in dogs with intracerebral lesions.

The centripetal nature of the cortical blood supply renders it plausible that the diminished amplitude of cerebral activity seen in our experimental animals with subdural and extradural lesions could be explained on the basis of interference with the vascularity of the cortex. The intracerebral lesions, however, for the most part lay well below the gray matter and seemingly produced little disturbance in cortical circulation. Alterations in major channels of blood supply are therefore probably not an important part of the mechanism for the production of abnormally slow high voltage activity.

Kennard and Nims [17] studied cortical ablation in monkeys and found a nonspecific decrease in amplitude and frequency of electrical activity which paralleled the development of postoperative edema. These ablations are not entirely compar-

12. Murphy, J. P., and Dusser de Barenne, J. G.: Thermocoagulation of Motor Cortex Exclusive of Its Sixth Layer, J. Neurophysiol. **4**:147, 1941.

13. Kennard, M. A.: Effects on EEG of Chronic Lesions of Basal Ganglia, Thalamus and Hypothalamus of Monkeys, J. Neurophysiol. **6**:405, 1943.

14. Dusser de Barenne, J. G., and McCulloch, W. S.: Some Effects of Laminar Thermocoagulation upon the Local Action Potentials of the Cerebral Cortex of the Monkey, Am. J. Physiol. **114**:692, 1936.

15. Walter, W. G.: The Technique and Application of Electro-Encephalography, J. Neurol. & Psychiat. **1**:359, 1938.

16. Bishop, G. H.: The Interpretation of Cortical Potentials, in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1936, vol. 4, p. 305. Dusser de Barenne and McCulloch.[14]

17. Kennard, M. A., and Nims, L. F.: Effect on Electroencephalogram of Lesions of Cerebral Cortex and Basal Ganglia in Macaca Mulatta, J. Neurophysiol. **5**:335, 1942.

able to the space-occupying lesions studied here. On the other hand, their failure to find specific focal alterations may well have been due to the fact that the cortical leading in their acute experiments was performed with the animals under anesthesia, and that in their chronic experiments on unanesthetized preparations all records were taken from scalp leads. Anesthesia increases the difficulty of detecting focal changes resulting from injury, and we have observed in dogs under local anesthesia that electrocorticograms revealed focal abnormalities which were not detectable in the electroencephalogram taken with skull electrodes.

Kennard [18] studied dial-anesthetized monkeys after total decortication and observed ". . . 8-10 per sec. oscillations such as are normal in these animals." Obrador [19] found that the electroencephalogram was abolished by destruction of the hypothalamus in the cat under pentobarbital anesthesia. Such work has suggested that the electroencephalogram is dependent on subcortical structures. It is our opinion, however, that conclusions as to cerebral activity in anesthetized animals do not necessarily explain electroencephalographic phenomena in unanesthetized preparations. Even light barbiturate anesthesia produces an electroencephalographic pattern differing greatly from the electroencephalogram seen in normal, unanesthetized animals. Our own observations and those of Witwer and associates [20] suggest that interference with the afferent pathways to the cortex may eliminate certain potentials of sleep. We have also seen that subcortical lesions can in part abolish spindles associated with pentobarbital anesthesia from the electroencephalogram. Such evidence, therefore, seems to show that potentials directly dependent on deeper structures are only one component of the electroencephalogram. The electroencephalogram as recorded from the unanesthetized animal is in part dependent on activity in the cortex. Kennard's conclusion [18] that ". . . lesions confined to cortical tissue do not alter it [the electroencephalogram] even if an entire hemisphere is removed," has not been confirmed by our experience. This has been true both in the case of lesions causing pressure on the cortex and in the cases of a hemidecorticate dog and a congenitally hemidecorticate child that we have studied. In the latter cases our observations agree with those of Ten Cate and associates,[21] who found that the record from the normal side in hemidecorticate dogs, cats and rabbits was several times as great as that on the side of the decortication. Their experiments demonstrated that the cortex is essential for the normal electroencephalogram as recorded from the scalp.

In our experiments, pressure from within the white matter produced abnormally slow potentials of high voltage, whereas pressure on the cortical layers from without did not. It therefore seems that some alteration in fiber connections to the cortex may favor the appearance of slow activity, but it does not necessarily mean that the white matter is the point of origin for these potentials. It is possible that delta activity could arise either as a result of disturbance of afferent pathways to the cortex or from apparently reversible changes in cortical neurons, not demonstrable with common histologic methods.

## CONCLUSIONS

High voltage slow (delta) waves were seen characteristically in the electroencephalogram of dogs with subcortical, space-occupying lesions. Such changes at their height resembled the electroencephalographic alteration seen in some cases of intracerebral, space-occupying lesions in man.

Disappearance of normal rapid activity and flattening of the electroencephalogram were seen with subdural and extradural space-occupying lesions in the dog.

Minor shifts in electrode placement can greatly alter the amount of abnormality seen in the electroencephalogram in cases of focal damage to the brain.

The electrocorticogram is a more sensitive record of abnormal brain potentials than is the electroencephalogram obtained by leading from the skull in dogs.

The electroencephalographic alterations caused by space-occupying lesions are of a reversible nature if the lesion is of fixed dimensions.

The electroencephalogram of the unanesthetized waking dog is in part of cortical origin. Brain potentials seen in sleep and during pentobarbital anesthesia may be controlled by subcortical mechanisms.

Harvard Neurological Unit, Boston City Hospital.

18. Kennard, M. A.: Electroencephalogram of Decorticate Monkeys, J. Neurophysiol. **6**:233, 1943.

19. Obrador, S.: Effect of Hypothalamic Lesions on Electrical Activity of Cerebral Cortex, J. Neurophysiol. **6**:81, 1943.

20. Witwer, E. R.; Derbyshire, A. J., and Corrigan, K. E.: Application of Some New Technics to Study of Brain Tumors, Radiology **41**:130, 1943.

21. Ten Cate, J.; Walter, W. G., and Koopman, L. J.: Electroencephalography After Removal of the Occipital Cortex, Arch. néerl. de physiol. **24**:153, 1939; Electroencephalography in Rabbits After Removal of Neopallium, ibid. **24**:578, 1940; Electroencephalography on Cats After Removal of Neopallium, ibid. **25**:27, 1940; Note on Electro-Encephalography of Brain Stem and Cerebellum of Cats, ibid. **25**:51, 1940.

# Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

## Anatomy and Embryology

ANATOMIC VARIATIONS OF THE LATERAL AND SIGMOID SINUSES. JULES G. WALTNER, Arch. Otolaryng. **39**:307 (April) 1944.

Waltner reports a hitherto unknown anomaly of the sigmoid sinus.

A 65 year old patient was operated on for septic thrombophlebitis of the right transverse sinus, but the sigmoid sinus could not be located; the patient died of purulent meningitis due to pneumococci of type III, which originated from a deep epidural abscess of the right posterior fossa. Autopsy revealed the following anatomic features: The left lateral and sigmoid sinuses were large, ended in a large jugular bulb and produced a deep groove in the left occipital and temporal bones. The left superior and inferior petrosal sinuses were normal. The right lateral sinus was narrow and barely admitted a probe. The right sigmoid sinus could not be found, and there was no evidence of a groove in the temporal and occipital bones. The superior petrosal sinus was normal and connected the narrow lateral sinus with the cavernous sinus. The inferior petrosal sinus was wider than usual, communicated regularly with the cavernous sinus and laterally ended in a pouch, which occupied the place of the jugular bulb and opened into a narrow internal jugular vein.

The author points out that variations of the lateral and sigmoid sinuses are independent of each other because these structures are developed from separate anlages and at a different stage of fetal life. A normal sigmoid sinus or a normal lateral sinus may each be present with the other sinus absent. The sigmoid sinus shows greater constancy and fewer variations than does the lateral sinus. This could be explained by the fact that the lateral sinus has to adapt itself to the increasing size and changing form of the surrounding structures, for example, the brain and the otic capsule. Thus, the lateral sinus is more likely to be interfered with in its development than is the sigmoid sinus. The latter is located close to the base of the brain from the very beginning of its development.

RYAN, M. C., A. U. S.

## Physiology and Biochemistry

THE ELECTROSHOCK CONVULSION SYNDROME. PAUL H. WILCOX, Am. J. Psychiat. **100**:668 (March) 1944.

Wilcox describes in detail the seizure picture encountered in electric shock therapy, dividing the seizure into (1) the tonic phase, (2) the clonic phase, (3) the atonic phase, (4) the stuporous period and (5) the postconvulsive mental state. He concludes that the electric shock convulsion is the result of integrated activity of a cortical area near the fissure of Rolando and is essentially a pyramidal tract syndrome. This conclusion is based on the following observations: (1) The most efficient shocks were those produced by stimulation near the fissure of Rolando; (2) the tonic pattern appeared to be the result of generalized excitation of the cortex, since there was a universality of muscular contraction; (3) a patient with a lesion of the pyramidal tract involving one leg had less strong contractions in that extremity, evidence that lesions of the pyramidal tract modify the seizure pattern; (4) disease of the extrapyramidal tract did not modify the convulsive pattern in a patient with all the classic signs of advanced postencephalitis; (5) autonomic excitation appeared to be a secondary phenomenon, since incontinence occurred not in the tonic or the clonic phase but in the stuporous period; (6) no simple medullary syndrome occurred, as indicated by changes in respiration and pulse; (7) strength-duration curves for threshold stimulation can be determined for electric shock, and (8) sodium amytal raised the convulsive threshold. Wilcox states that this drug acts primarily on the higher cortical levels of integration and concludes that the trigger zone is probably at a "fairly high level of cortical integration."

The author concludes that the trigger zone plays a central role in all convulsions and that epilepsy is due to an overflow of excess irritation from some other area. The complex character of convulsive patterns in epilepsy may be due to the modifying influence of the cerebral dysrhythmias. FORSTER, Philadelphia.

THE STRUCTURAL IDENTITY OF THE PAIN SPOT IN HUMAN SKIN. G. H. BISHOP, J. Neurophysiol. **7**: 175 (May) 1944.

Bishop mapped the most sensitive points for evocation of pain on his own forearm. These areas were then studied by chemical or surgical denudation to various depths, followed by electrical stimulation, not only after denudation but during the course of regeneration. Epithelium was found to regenerate from the base of each hair follicle, and a nerve twig containing pain fibers approached the epithelium near each group of hair follicles. This twig was distributed to an area containing one pain spot. The extreme sensitivity of the central high point in a unit pain area may be correlated with its position directly over the pain twig. Thus, terminals of several fibers may be activated by a stimulus at one point. Bishop found that the growing ends of pain fibers in the skin are more sensitive to mechanical stimulation and less sensitive to electrical stimulation than are their final sensory endings. However, various qualifying features are concerned in the conditions under which the stimuli are applied. Dendritic fibers were observed to invade the regenerated epithelium at about the stage at which nerve fibers are approaching it and appeared first in the regions overlying the nerve twigs. Bishop states that it is not clear whether this indicates a functional relation or merely a relation to the stage of development of epithelium from the follicles. He notes that accounting for the uniqueness of individual pain spots on a structural basis does not explain the sensory localization of pain. FORSTER, Philadelphia.

PROGRESSIVE ASCENDING PARALYSIS IN DOGS DUE TO DEFICIENCY OF A VITAMIN B COMPLEX FACTOR FOUND IN YEAST. SUSAN GOWER SMITH, Science **100**:389 (Oct. 27) 1944.

Smith reports her observations on 38 dogs which received a synthetic vitamin B complex–free diet, composed of casein (water and alcohol extracted), 40 per cent; sucrose, 36 per cent; cottonseed oil, 18 per cent; cod liver oil, 2 per cent, and mineral salts, 4 per cent. This diet was altered in the case of the positive control animals to contain 10 per cent dried brewers' yeast as a source of the vitamin B complex. The other animals had their vitamin B complex requirement met by administration of seven or eight of the following synthetic vitamins: (1) thiamine hydrochloride, (2) riboflavin, (3) pyridoxine, (4) nicotinic acid, (5) pantothenic acid, (6) paraaminobenzoic acid, (7) inositol and (8) choline.

The incidence of progressive ascending paralysis varied considerably with the different deficiencies, but it was greatest in the animals receiving all the synthetic vitamin B complex factors listed, 11 of the 12 becoming paralyzed. The paralysis was at first spastic and later became almost completely flaccid. The dogs died quickly if untreated.

Paralysis is regularly prevented by brewers' yeast and is cured by a water extract of yeast. It responded promptly (eight to twelve hours) to biotin therapy in seven attacks in 4 dogs. The biotin was dissolved in isotonic solution of sodium chloride U. S. P. and administered subcutaneously. The therapeutic dose is approximately 100 micrograms per kilogram of body weight.

GUTTMAN, Philadelphia.

THE CHEMISTRY OF CEREBRAL TUMOURS AND OF CEREBRAL CYST FLUIDS. J. N. CUMINGS, Brain **66**:316, 1943.

Cumings studied the water, potassium, sodium chloride and phosphorus contents of 47 tumors of the brain and of 5 tumors of the spinal cord, as well as the nucleoprotein, phospholipid and acid-soluble phosphorus contents of 38 tumors of the brain and the fluid of 26 cerebral cysts and 1 subdural hematoma. Of the tumors, medulloblastoma had the highest water content, and spinal chordoma the least. An elevated phosphate content of tumors appeared to be related to a tendency to degenerate. The amount of nucleoprotein varied, probably in accord with the degree of cellularity of the particular tumor. Nearly all the cysts contained a high concentration of acid-soluble phosphorus. A moderate amount of phospholipids appeared in most cysts, notable exceptions being the subdural hematoma, pituitary adenoma and suprasellar cyst. From these studies Cumings concludes that tumor cysts probably occur by breakdown of tumor and cerebral tissue.

FORSTER, Philadelphia.

PROPOGATION OF EPILEPTIFORM IMPULSES IN THE BRAIN: I. ROLE OF THE CORPUS CALLOSUM. SIXTO OBRADOR ALCALDE, Bol. d. Lab. de estud. med. y biol., Mexico **1**:29 (April) 1942.

Obrador Alcalde stimulated the cerebral cortex of cats with an alternating electrical current for periods of ten seconds at intervals of two minutes. The corpus callosum was sectioned in 11 animals. There was no significant change in the nature of the induced convulsive seizures after section. In only 1 animal were the convulsions less intense in the limbs ipsilateral to the side of the brain which was stimulated. In a few other animals there was some variation in the convulsive threshold with slight decrease in intensity of the convulsions. There was no significant variation in the pattern of the attacks. The corpus callosum therefore does not appear to be essential in transmission of epileptigenous impulses from one side of the brain to the other.

SAVITSKY, New York.

## Neuropathology

SIMMONDS' DISEASE WITH THERAPEUTIC RESPONSE TO HORMONE THERAPY FOR FOUR YEARS: REPORT OF A CASE WITH NECROPSY FINDINGS. WARD DARLEY, ROBERT W. GORDON and KARL T. NEUBUERGER, Ann. Int. Med. **21**:890 (Nov.) 1944.

Darley, Gordon and Neubuerger report the case of a man who first came under their observation when he was 44 years of age. The results of clinical and laboratory studies were characteristic of Simmonds' disease, which had been present for twenty-three years. The administration of chorionic gonadotropin produced a therapeutic response for four years.

Necropsy revealed complete obliteration of the pituitary, pronounced sclerosis of the thyroid and testes and atrophy of the prostate and adrenals, together with moderate degenerative changes in the brain, particularly in the thalamus and the interbrain.

GUTTMAN, Philadelphia.

LATE CEREBRAL SEQUELAE OF RHEUMATIC FEVER. WALTER L. BRUETSCH, Arch. Int. Med. **73**:472 (June) 1944.

Bruetsch reports his observations in 500 consecutive and unselected necropsies on patients with mental illness. Rheumatic cardiovalvular changes were noted in 5 per cent of the subjects. Of the group of 171 patients with dementia paralytica, rheumatic valvular disease was present in only 1.7 per cent, while in 100 patients with schizophrenia the incidence was 9 per cent. Of 549 female patients admitted, 8.1 per cent had evidence of rheumatic infection. The incidence in 502 male patients was 2.6 per cent. The ratio of the incidence in men to that in women was approximately 1:3. It is estimated that there are about 1,000,000 persons with rheumatic heart disease in this country—or less than 1 per cent of the total population. The high prevalence of rheumatic cardiac disease among patients with mental illness suggests the possibility of a direct relation between rheumatic fever and mental symptoms.

Bruetsch states that a late sequel of rheumatic fever is obliterating endarteritis, which usually develops while the patient is otherwise in good health. This vascular process may produce gross and microscopic infarctions in the gray matter of the brain, with consequent mental symptoms. This change represents a chronic infectious process, similar to rheumatic heart disease, and has been termed "rheumatic brain disease." Other late cerebral sequelae of rheumatic fever are encephalitis and cerebral embolism, the latter occurring most often during auricular fibrillation in patients with mitral stenosis.

GUTTMAN, Philadelphia.

ENCEPHALITIS COMPLICATING VIRUS PNEUMONIA. HELEN INGLEBY, Arch. Path. **37**:359 (June) 1944.

In a patient aged 58 who died with symptoms suggestive of "acute encephalitis" complicating virus pneumonia, inclusion bodies similar to those described by Adams were found in the epithelium of the bronchi and

other organs. Numbers of them were noted in all parts of the brain—in the nerve cells, the neuroglia cells and the perivascular zones. Vascular thrombosis and acute degeneration of nerve cells were present. Perivascular exudate was not a feature of the disease.

WINKELMAN, Philadelphia.

MYASTHENIA GRAVIS. FRED S. PREUSS and SEABURT GOODMAN, Arch. Path. **37**:389 (June) 1944.

In a typical case of myasthenia gravis of about six weeks' duration in a patient aged 59 in which neostigmine was of no value, autopsy showed thymoma (marked hyperplasia of the thymus), hemangioma of the liver, a fibromyoma of the lower third of the esophagus, nodular hypertrophy of the prostate gland and neurofibromatosis. There is no similar case in the literature of a combination of neurofibromatosis and myasthenia gravis.

WINKELMAN, Philadelphia.

AMEBIC COLITIS COMPLICATED WITH ABSCESS OF THE BRAIN. BELA HALPERT and J. D. ASHLEY JR., Arch. Path. **38**:112 (Aug.) 1944.

Among the complications of amebic colitis, abscess of the liver is frequent, the incidence varying from 3.5 per cent, in living patients, to over 42 per cent, in patients with necropsy. Involvement of the brain is a rare complication and is usually associated with similar involvement of the liver and lungs or of both these organs. To date, 61 cases of amebic abscess of the brain have been reported. The case reported by Halpert and Ashley is the fifth in the literature in which abscess of the brain occurred without involvement of the liver and lungs.

WINKELMAN, Philadelphia.

THE CENTRAL NERVOUS SYSTEM IN DIPHTHERIA. A. B. BAKER and H. H. NORAN, J. Nerv. & Ment. Dis. **100**:24 (July) 1944.

The effects of diphtheria on the nervous system are due to the action of the powerful exotoxin elaborated by the bacillus. Toxic mononeuritis or multiple neuritis is a not uncommon neurologic complication, while involvement of the central nervous system is rare, appearing as toxic delirium, toxic encephalitis or hemiplegia, the paralysis being the result of vascular occlusion due to an embolus originating from a cardiac thrombus secondary to myocardial damage. Hemiplegia usually appears late in the course of the disease, during the third to the fifth week. The authors present the case of a man aged 64 who had had postdiphtheritic hemiparesis since the age of 12 years. At the age of 52 he had an acute confusional state; after he recovered from this, he was psychotic until his death, from a head injury, at the age of 64. Coronal sections of the brain revealed a large multiloculated cystic area involving the left parietal and temporal lobes.

CHODOFF, Langley Field, Va.

ALLERGIC BRAIN CHANGES IN POST-SCARLATINAL ENCEPHALITIS. A. FERRARO, J. Neuropath. & Exper. Neurol. **3**:239 (July) 1944.

Ferraro reports the case of an 11 year old white boy in whom seizures developed two weeks after an attack of scarlet fever. The seizure was followed by temper tantrums, and within a few months the patient became "dull, stupid, unable to think coherently, and was awkward with his hands." Six months after the illness with scarlet fever the lad was institutionalized. He was distractable and showed impairment of attention and comprehension, and tests of his intellectual ability indicated deterioration. Speech was slurred; the deep reflexes were overactive, and there was a coarse tremor of the outstretched hands. He became dull, retarded and unclean in his habits. Typhoid vaccine was administered on two occasions. Later in the course of the illness he had a febrile illness for eight days, with fever, incontinence, stupor and frequent nasal hemorrhages. Involvement of the central nervous system was indicated by nystagmus, bilateral internal strabismus, overactive deep reflexes, ankle clonus and intermittent twitchings of the right arm and leg. Later the arms became flexed at the elbows, and both feet exhibited a strong plantar flexion. There was increased tone of the muscles of the jaw, so that the mouth could not be opened. Repeated lumbar punctures revealed an elevated spinal fluid pressure and a colloidal gold curve of 5555220000.

During the last months of his illness tube feedings were necessary. The limbs became spastic, and there were constant nystagmoid movements of the eyes. A Babinski sign was present bilaterally. Pneumonia developed, and death occurred about fourteen months after the onset of the acute exanthematous illness.

Ferraro also mentions the clinical history of a case previously reported by Winkelman. Anatomic study of tissue in both cases revealed the presence of a perivascular reaction, which was both lymphocytic and histiocytic. Lymphocytes prevailed in the less involved areas, whereas in the more severely damaged regions lymphocytes were surrounded with collars of compound granular corpuscles. Mixed with the lymphocytes here and there, especially in the areas of most intensive reaction, were elements presumably of mixed hematogenous and histiocytic origin, having a tendency to fuse together.

One interesting feature of the exudate was the extension of the microglial reaction, which could be traced from the blood vessels within the surrounding nerve parenchyma. The reaction of the microglia passed through all stages of transition to that of the compound granular corpuscle. A stage worthy of mention in this transformation was the loss of reticular appearance while the protoplasm was still compact, although the cell assumed a polygonal outline. Also, the vascular and the perivascular reaction were unusually intense, and both hematogenous and fixed elements seemed to participate. At times edema and hemorrhage were observed. Thrombi, softening and necrosis were also present on occasion.

Ferraro mentions three possible explanations of the pathologic process: a true inflammation, a degenerative disease process or an allergic reaction (hyperergic inflammation). He is inclined to view the process as an allergic reaction.

GUTTMAN, Philadelphia.

## Psychiatry and Psychopathology

CIVILIAN WAR NEUROSES AND THEIR TREATMENT. FELIX DEUTSCH, Psychoanalyt. Quart. **13**:300, 1944.

Deutsch reports on the activities and findings of the psychiatric clinic of the Boston Psychoanalytic Institute. The objective of the clinic is the treatment of mentally ill persons rejected by the armed forces and the development of an emergency psychotherapy based on psychoanalytic principles. Since October 1942 the clinic has accepted for treatment 61 patients—45 men and 16 women. Fifty per cent of the men were the youngest of the family, the only child or the single boy among girls. Five patients had an acute and 56 a chronic psychosis. The disorder of 26 patients was diagnosed as psycho-

neurosis, that of 15 as a character disorder, that of 10 as a psychosomatic disturbance and that of 10 as a borderline state.

The civilian war neurosis is a family neurosis, centered around the member directly involved in the service, who either is then the contagious member or becomes the target and victim of the neurotic reaction of the environment. The main obligation of the soldier is to be aggressive at the right moment with the proper weapons, in common with his comrades. The aggressive tendency can be directed against external objects. This process increases his morale; i. e., it diminishes his fear of danger from without. The civilian, also, must acquire morale, the will to resist aggression, and must develop hostile feelings against outside forces, without the possibility of putting them into action. These hostile feelings are cultivated and increased by restrictions, deprivations and frustrations, for all of which the enemy is held responsible, so that there is no escape and no permissible response except that which is inherent in morale. The war situation so influences each civilian that he struggles to become a man while some one holds him back or so that he resists becoming a man while some one pushes him. The central factor is the fear of his own aggression. Other persons involved act by contagion or as participants in the conflict. In short, the civilian becomes ill because he cannot acquire the new personality, viz., the demand for increased aggression, which is in conflict with inertia and the fear of acting out aggressive impulses which the war asks of him.

The treatment of civilian war neuroses has been divided into two parts. The patient is interviewed by the psychiatric social worker, who gathers the facts of the medical and social history and makes and maintains all contacts with members of the family and the referring institutions. The psychoanalyst has personal contact only with the patient. Two or three of the patient's relatives and friends are treated as patients by other analysts if they are seriously involved in the case. The psychotherapy is directed essentially toward the conflict between passivity and activity, hostility and peacefulness, aggression and submission. Success depends on the redistribution of the libidinal factors which produce narcissistic self esteem, the capacity to develop aggression, the ability to direct that aggression adequately and appropriately and the courage demanded by independency and activity.

PEARSON, Philadelphia.

THE PHYSICAL EXAMINATION OF TWO THOUSAND CASES OF NEUROSIS. H. G. MCGREGOR, J. Neurol. & Psychiat. **7**:21 (Jan.-April) 1944.

Of 2,288 consecutive patients admitted to a military hospital, McGregor found that 3.4 per cent showed evidence of organic disease which was mistaken for a neurosis. In the remaining 2,210 patients the organic element was minimal. Of these, the patients with psychosomatic neuroses form the main consideration in this paper. In 14 per cent of these patients the blood pressure showed systolic and diastolic readings greater than 140 and 90 mm. These readings, however, were reduced to approximately normal with rest and confidence, except in the cases of 7 patients in whom abnormalities were discovered on examination of the retina and urine. There was no relation between the height of the blood pressure and the degree of anxiety. Of 150 men with symptoms of the effort syndrome, 29 showed a deceleration rate in excess of three minutes, but in every case a normal exercise tolerance was recorded. The increased deceleration rate was probably the result of emotional factors. The specific location of psychosomatic symptoms is influenced by physical and psychologic factors. Only the former were analyzed, with the following results: (1) Heredity: Once a neurosis became established in a family, succeeding generations tended to suffer from a similar one. (2) Constitution: Seventy-one per cent of the patients with psychosomatic disturbances showed a fundamental timidity or apprehensiveness in their output of physical energy, which had existed all their lives. (3) Incidence of previous disease or trauma: Antecedent disease played a large part as a predisposing factor, while remote trauma was common, particularly in cases of backache and headache, the localization of the neurotic symptoms being usually in the same position as the trauma. (4) Physique-personality: Although no systematic study was undertaken by the author, these factors were considered of significance in the specific clinical picture. All these factors were regarded merely as directing the location of the symptoms once the ultimate causes of the neurosis had produced a favorable psychologic status.

MALAMUD, Ann Arbor, Mich.

## Meninges and Blood Vessels

CAVERNOUS-SINUS THROMBOPHLEBITIS — REPORT OF A CASE WITH MULTIPLE CEREBRAL INFARCTS AND NECROSIS OF THE PITUITARY BODY. AVERY D. WEISMAN, New England J. Med. **231**:118 (July 27) 1944.

Weisman reports the case of a 13 year old boy in whom thromophlebitis of the cavernous sinus developed subsequent to a furuncle on his nose. During the course of the illness, a total of twenty-four days, the patient exhibited edema about the left eye with proptosis. He was comatose much of the time. When aroused, he understood simple commands but was unable to speak. There was right hemiplegia with overactive deep tendon reflexes and an equivocal Babinski sign. Also, right homonymous hemianopsia was present, and funduscopic examination revealed edema and hyperemia, with blurring of the nasal margins of the disks. There was no response to painful stimuli over the right side of the face. The patient had one generalized seizure. The cerebrospinal fluid was under increased pressure and was yellowish and cloudy, and the white cell count was 2,900 leukocytes, of which 1,450 were polymorphonuclear leukocytes and 750 were erythrocytes. The total protein measured 534 mg.; the sugar, 57 mg., and the chlorides, 639 mg. per hundred cubic centimeters. A hemolytic Staphylococcus aureus was grown from the spinal fluid, as well as from the blood. Sulfadiazine therapy was of little avail, and trephination on the left side failed to reveal evidence of a subdural abscess. The patient died twenty-four days after the onset of his illness.

The significant findings at necropsy were as follows: thrombophlebitis of the left and right cavernous sinuses, the left superior petrosal sinus and the ophthalmic veins; bilateral orbital abscesses; basilar purulent leptomeningitis; infarction of the pituitary gland; small, recent cerebral infarcts, involving the left frontal, parietal and parieto-occipital lobes; cerebellar pressure cone; internal hydrocephalus; fibrinopurulent pleuritis with empyema (right).

Although several thrombosed arteries were found, no source of the thrombosis could be ascertained. The

pathologic findings provide an explanation of the clinical picture. The possibility of hypopituitarism as a sequel of thrombophlebitis of the cavernous sinus is suggested.

GUTTMAN, Philadelphia.

## Diseases of the Brain

BRAIN LESIONS ASSOCIATED WITH EXPERIMENTAL "EPILEPTIFORM" SEIZURES IN THE MONKEY. S. EUGENE BARRERA, LENORE M. KOPELOFF and NICHOLAS KOPELOFF, Am. J. Psychiat. **100**:727 (May) 1944.

Barrera, Kopeloff and Kopeloff report the neuropathologic findings in Macacus rhesus monkeys in which convulsive seizures had been induced by a single application to the cerebral motor cortex of chemical and immunologic agents. With this technic, the authors induced not only acute manifestations but a state of chronic convulsive reactivity. Application of the agents produced a chronic progressive meningocortical scar. The scars developed in animals which had exhibited seizures as well as in those which had not had convulsive manifestations. The degree of pathologic alteration could not be correlated with the development or frequency of seizures. Barrera, Kopeloff and Kopeloff conclude that the pathologic changes produced were insufficient in themselves to account for the convulsive manifestations.

FORSTER, Philadelphia.

SPASMODIC TORTICOLLIS. RALPH M. PATTERSON and SAM C. LITTLE, J. Nerv. & Ment. Dis. **98**:571 (Dec.) 1943.

Patterson and Little review the literature and present new data on the subject of spasmodic torticollis based on a study of 103 cases of the condition. The muscles most commonly involved are the sternocleidomastoid on the side opposite the deviation and the trapezius muscle and the deep muscles of the neck on the same side. Usually muscles on both sides of the neck are implicated. The pathways concerned with mediation of the abnormal movements are probably in the vestibular and the extrapyramidal systems while in certain cases in which pronounced reflex synergism among the muscles of the hand, neck and eye is shown, tracts originating in the inferior olivary and the dorsal accessory olivary nuclei may be concerned.

The average age of onset was 37.8 years, and in 72 per cent of cases the appearance of symptoms was insidious. Pain was a frequent complaint, appearing in 66 per cent of cases. The importance of the "antagonistic gesture" in relieving the spasm was borne out in the study, and the authors believe that proprioceptive impulses from the arm used in the movement were of more importance than the side of the chin or the face to which the stimulus was applied. The disorder was influenced by numerous stimuli of various types. Sleep almost invariably abolished the spasms, while emotional stress aggravated them.

Neurologic abnormalities were present in 48 per cent of the cases. Changes in the cranial nerves, reflexes and sensations were all present. In only 6 of the 21 cases in which psychiatric evaluation was carried out were the findings considered significant. Lesions of the cervical vertebrae and cervical muscles were considered to be either incidental or secondary, while vestibular disorders appeared to be of significance in certain cases. In 5 of the cases there was a definite antecedent history of encephalitis.

The authors found that, contrary to common belief, the course of the disorder was not invariably progressive. A surprising number of patients showed considerable improvement or arrest of the condition.

Necropsy reports have failed to reveal any specific localization for the lesions responsible for spasmodic torticollis. The etiologic factors in the condition have been much debated, with the adherents of psychogenic and those of organic causation in disagreement. The authors feel that organic causes were paramount in their cases, and they minimize the importance of psychogenic factors. They feel that the pathophysiologic substratum of the disorder is basically in the extrapyramidal connections, with the vestibular mechanisms acting as a conditioning component. A combination of lesions is probably necessary, such as destruction of portions of the extrapyramidal system as a result of encephalitis and vestibular involvement, such as may accompany otitis media.

Methods of treatment have included use of mechanical restraints, heat and massage, electrical stimulation and galvanism; removal of foci of infection; administration of drugs, and psychotherapy. All of these measures were largely unsuccessful in the cases reported. Surgical treatment ranged through tenotomy of the sternocleidomastoid muscle, section of the spinal accessory nerve, multiple myotomy of the cervical muscles and rhizotomy of the posterior divisions of the upper cervical nerves. The procedure of combined bilateral extradural rhizotomies and section of both eleventh nerves has been successful in some cases. The method most commonly used at present was originated by Dandy and consists of bilateral section of the first, second and third anterior and posterior cervical nerve roots plus peripheral section of both spinal accessory nerves.

CHODOFF, Langley Field, Va.

ARTERIOVENOUS ANEURYSM OF MIDBRAIN AND RETINA, FACIAL NÆVI AND MENTAL CHANGES. R. WYBURN-MASON, Brain **66**:163, 1943.

Wyburn-Mason gathered from the literature 27 cases of retinal arteriovenous aneurysm or similar anomalies and found that in 22 of them there was evidence of an intracranial arteriovenous aneurysm. In the 14 of the 22 cases in which it was posssible to draw deductions the intracranial lesion was thought to be in the midbrain. Of the 20 cases of arteriovenous aneurysm, which included 6 of the series of 9 cases the author reported, retinal abnormalities were present in 14. When the condition was fully developed, the abnormal vessels extended from the retina as a tract of reddish vascular tissue on one side, covering and permeating the optic nerve, chiasm and tract and lying above the cavernous sinus. The mass of abnormal vessels extended posteriorly to reach the dorsum of the midbrain and permeated the quadrigeminal bodies, the brachia conjunctiva and the red nucleus. The mass of vessels sometimes extended anteriorly into the hypothalamus and the pulvinar, posteriorly into the cerebellum or laterally into the choroid plexus. Histologically, the affected portions of the brain consisted of many tortuous and dilated blood vessels, having the appearance, for the most part, of arteries. In these vessels degenerative changes sometimes occurred, particularly in the intima and elastica. Hydrocephalus was observed in all cases in which autopsy was done. There was an increase in the size and number of the blood vessels of the skull. Proptosis usually occurred in the affected eye. The vascular lesion of the eye was usually ipsilateral to the lesion in the midbrain and consisted of a direct arteriovenous communication, most frequently in the inferior temporal vessels. Vascular nevi were described in

several cases; they were usually in the trigeminal distribution and always ipsilateral. Other congenital anomalies were present in a number of cases. The anomalous vessels were considered of congenital origin. Wyburn-Mason correlated the development of the cerebral vascular system, as described by Streeter, with the development of this condition, concluding that any inherent defect of the vessels of the mesenchyme at Streeter's third stage would affect the vessels of the brain stem, retina and skin of the face.

Wyburn-Mason found that symptoms occurred in almost every case before the age of 30 and that the condition was slightly more common in males. The appearance of symptoms depends apparently on thrombosis or hemorrhage in the anomalous vessels; either visual or cerebral symptoms may be the first manifestation. Visual failure may be sudden or gradual. The lesions in the midbrain may give rise to a variety of symptoms, including subarachnoid hemorrhage, hydrocephalus or symptoms referable to the midbrain. Whatever the mode of onset, there is always evidence of a lesion in the midbrain, and the Weber syndrome predominates in frequency. Other cranial nerves or structures of the midbrain may be involved, however, and in some cases attacks resembling diencephalic fits occur. In late cases signs of arteriovenous aneurysm appear. Psychosomatic symptoms were divisible into temporary and permanent. Temporary symptoms include delirium, hallucinosis, disorientation, malaise and sleep disturbances. Permanent mental symptoms were divisible into disturbances of memory and intelligence and psychiatic reaction types. In some instances there was an increase in the pressure of the cerebrospinal fluid, and in most instances the total protein was elevated. Roentgenograms of the skull are usually normal but may show evidence of increased pressure, erosion of the apex of the petrous bone or shift of the pineal body. Air studies may reveal generalized hydrocephalus or yield evidence of a local tumor. Arteriography may give some indication of the nature of the pathologic process. Seven of Wyburn-Mason's 9 patients died. Roentgen therapy was found to be of no avail. Surgical treatment and the application of radon seeds to the sclera resulted in some improvement.

FORSTER, Philadelphia.

BLAST INJURY: NON-FATAL CASE WITH NEUROLOGICAL SIGNS. OLIVER GARAI, Lancet **1**:788 (June 17) 1944.

Garai reports the case of a young soldier thrown a few feet along the pavement by the blast of a bursting bomb. He had no appreciable external injury and did not lose consciousness or show retrograde amnesia; it was thought therefore that he had not suffered a concussion. At first the only neurologic sign was a dilated right pupil, which did not react at all to light and only slightly in accommodation. Two or three days after the accident an extensor plantar response developed on the left side, but he was well clinically. He lost the extensor response in two weeks; but the pupil was still sluggish in reaction to light a year later, although the response in accommodation had returned almost at once.

The spinal fluid was normal in all respects. The electroencephalogram showed a dominant 9 per second frequency of moderate voltage forty-eight hours after injury, with diffuse minor irregularities of rhythm in all areas, particularly a 4 to 6 per second frequency in the parietal region. In the following days and weeks, a slow rhythm appeared in the left frontal area and then gave way to small bursts of slow activity in all areas, with less evidence of a single focus. A year later this rhythm still persisted.

The author believes, since there was no concussion, that "the intracerebral lesion is best explained on the basis of altered hydrostatic pressure in the cerebral veins due to blast effects on the trunk." Thus, the changes in the right pupil and the signs referable to the pyramidal tract on the left side suggested a periaqueductal lesion in the midbrain, "possibly hemorrhagic."

MCCARTER, Philadelphia.

PAROXYSMAL AND POSTURAL HEADACHES FROM INTRAVENTRICULAR CYSTS AND TUMORS. WILFRED HARRIS, Lancet **2**:654 (Nov. 18) 1944.

Harris reports 3 cases of pedunculated tumor blocking one foramen of Monro, associated with sudden paroxysmal headache on change of posture of the head. Even more striking was the sudden relief of the paroxysmal headache with change of posture. The author stresses the character of the headache and the suddenness of its onset and disappearance, especially if changes of posture produce or relieve the headache suddenly, as diagnostic signs of a valvular intraventricular lesion. He emphasizes the fact that in many recorded instances, and in his own observations, cysts and tumors of the third and the lateral ventricles give no physical signs beyond the so-called classic triad of headache, vomiting and papilledema. It is therefore probable that in many such cases no autopsy has been done and that the incidence of these lesions is much greater than the published records indicate. Harris concludes that intermittent headaches, sometimes persistent for ten years, may be due to an intraventricular cyst or tumor. The onset and disappearance of the headaches are often sudden, and the sudden production or relief of headache with change of posture is a pathognomonic sign of the ball-valve action of such cysts or tumors in blocking one or both of the foramens of Monro. Colloid cysts of the third ventricle appear to be the commonest variety and grow from the anterior part of the roof of the third ventricle. They are nonmalignant, and, when approached through a hypophysial flap, they are not difficult to remove completely.

YASKIN, Camden, N. J.

## Cerebrospinal Fluid

SOME OBSERVATIONS ON THE CEREBROSPINAL FLUID IN CLOSED HEAD INJURIES. J. H. PATERSON, J. Neurol. & Psychiat. **6**:87 (July-Oct.) 1943.

Paterson investigated the cerebrospinal fluid in 300 cases of acute closed head injuries uncomplicated with extradural or subdural hematoma. In nearly two thirds of the cases the cerebrospinal fluid pressure was normal, but there was a relatively higher proportion of cases of the more severe injuries in which the pressure was increased. In such cases there was a natural return to normal levels within one week of injury. These observations indicate that the pressure does not play an important role in the symptoms of acute injury. In 120 of the 300 cases blood in significant quantities was found in the cerebrospinal fluid at the initial puncture, but the clearance of blood was completed within one week of injury without repeated punctures, and the latter did not hasten the rate of clearance. The frequency of blood in the spinal fluid was directly proportional to the severity of the injury. No definite correlation existed between the level of pressure and the red blood cell count except when considerable bleeding had occurred, in which case there was usually a rise in pressure. There was a fairly close, but not invariable, relationship between the amount of blood in the cere-

brospinal fluid and the mental state of the patients. Alterations in consciousness were attributed by the author either to hemorrhage from cortical lacerations or to interference with the function of the midbrain.

MALAMUD, Ann Arbor, Mich.

## Muscular System

MYOTONIC DYSTROPHY. B. B. MONGILLO and MAX SEROG, J. Nerv. & Ment. Dis. **99**:906 (June) 1944.

Mongillo and Serog review the literature on myotonic dystrophy. This condition differs from Thomsen's disease in the restriction of the myotonic reaction to a few muscles, the development of atrophies, the appearance of the disorder after the age of 30, the decreased strength or absence of tendon reflexes and the presence of extramuscular phenomena, such as cataract, testicular atrophy and baldness. In some cases the presence of tabiform ataxia has been correlated with degeneration of the posterior column. The myotonia tends to precede the development of the selective atrophy of the facial muscles, the sternocleidomastoid muscles, the muscles of the forearm and thigh and the dorsiflexors of the feet. Electromyographic studies have revealed the persistence of action currents after the cessation of voluntary muscle contraction, thus indicating the neurogenic, rather than the myogenic, nature of the disorder. Harvey has suggested that the favorable effect of quinine is due to a curare-like action, which decreases excitability of the end plates. In cases of atrophic myotonia associated with testicular atrophy, the use of testosterone propionate, in addition to quinine, has been favorably reported on.

The authors report a typical case of atrophic myotonia which they had under observation for more than a year. After treatment with a combination of calcium, quinine and thyroid had proved ineffective, the patient was given a preparation of vitamin E (1 capsule three times a day), to which weekly injections of testosterone propionate were later added. Under this regimen his general condition and the function of some muscles were considerably improved. This finding suggests the reversible nature of some of the neuromuscular disturbances characteristic of the disease.

CHODOFF, Langley Field, Va.

## Congenital Anomalies

HEREDITARY ECTODERMAL DYSPLASIA. FRANCIS E. BRUNO and HUGO T. ENGLEHARDT, Ann. Int. Med. **20**:140 (Jan.) 1944.

Bruno and Englehardt report the case histories of 3 siblings with sparse hair of a fine texture and with nails of the fingers and toes which were short, thin and brittle and possessed a central concavity. In 2 of the cases the upper third molars were missing. The cases were regarded as examples of hereditary ectodermal dysplasia.

GUTTMAN, Philadelphia.

PARTIAL ALBINISM AND NYSTAGMUS IN NEGROES. L. J. A. LOEWENTHAL, Arch. Dermat. & Syph. **50**:300 (Nov.) 1944.

Loewenthal presents the case histories of 2 male Negroes with partial albinism. One was a "red" and the other a "yellow" Negro. Nystagmus of the congenital type was present in both patients. Nystagmus in albinos is not caused by gross deficiency in the eye, for each of the subjects had an amount of ocular pigment equivalent to that of a European brunet.

GUTTMAN, Philadelphia.

# Book Reviews

**Handbook of Psychiatry.** By Louis J. Karnosh, B.S., ScD., M.D., and Edward M. Zucker, A.B., M.D. Price, $4.50. Pp. 302. St. Louis: C. V. Mosby Company, 1945.

The authors of this handbook are substantially faithful to their stated purpose expressed in the preface, namely, that this book is "a valuable increment of the library of the physician and the medical student." The integration into the practicing physician's armamentarium of the modern concepts in the field of psychiatry will enhance his diagnostic, as well as his therapeutic, skill.

The chief merit of this book is in its comprehensive coverage, as well as in its simplicity and clarity of presentation.

Compressed into brief chapters are the salient features of such subjects as "Heredity and Mental Disease," "Structure of Personality" and "Defense Mechanism of Personality."

Uniquely, there are included such provocative discussions as the chapters on "Psychosomatic Medicine" and "Mental Hygiene." The latter subject, although dealt with somewhat tentatively, opens a vast field for exploratory investigation, with promises of fruitful results. It is impressive that the sociologic and environmental factors in early development are recognized as determinative of future mental patterns.

The sections on "Neuroses and Psychoses of War" and "Physical Therapy," as well as the section on "Occupational Therapy," are particularly timely.

The up-to-dateness of the book is evidenced by the inclusion of discussions of such modern technics in therapy as electric shock and the use of penicillin in treatment of neurosyphilis.

Of course, one cannot expect within the limits of this book and its ambitious scope, exhaustive treatment of any one subject. However, for readers who may be interested in a more thorough understanding of any part of the text, the authors have furnished excellent references and authorities.

I believe that this book is a welcome contribution to the growing psychiatric literature.

# Society Transactions

## PHILADELPHIA PSYCHIATRIC SOCIETY

HAROLD D. PALMER, M.D., *President, in the Chair*

*Regular Meeting, Nov. 10, 1944*

**Psychologic Factors in the Problem of Obesity.** DR. ROBERT R. SCHOPBACH and DR. ROBERT A. MATTHEWS (by invitation).

This paper is a preliminary report indicating some general psychologic trends observed in a group of 50 patients studied by the endocrine clinic group of the Jefferson Hospital. The endocrine, chemical, anthropometric, roentgenographic, psychometric and psychiatric aspects were investigated, but only the study of the psychiatric factors disclosed any material of clinical significance. In all but 5 or 6 patients psychogenic factors bore a close relationship to the onset and development of obesity. Since the group was so small, statistical analysis was not attempted, but certain type reactions were noted.

Mild anxiety states with much neuromuscular tension and some obsessive-compulsive tendencies were most common. Patients with such states, who described themselves as "the nervous type," usually suffered an additional trauma, such as worry over a son going overseas, a husband coming home drunk or some incident which threatened their security. Under such conditions there may be an increased urge to eat; and unless the urge is satisfied, the tension mounts and other somatic symptoms appear. In some cases this process was repeated at short intervals for weeks or months, while in others it occurred only after some particular stress. In some cases there was a more specific trauma, arising from the family constellation, pubertal problems, sexual maladjustment, pregnancy or the climacteric.

Many of the patients were vaguely aware of the relation between their desire for food and their nervous tension. Most, however, were unable to use that knowledge but required psychiatric help before they were able to remain comfortably on a diet. For some patients minimal psychotherapy was helpful. Ideally, however, repeated conferences are required.

DISCUSSION

DR. ROBERT A. MATTHEWS: When the study of obesity was instituted at Jefferson Hospital, a psychiatric survey was made. It was expected that emotional problems would be found in a fairly large percentage of patients, but it was a surprise to discover that most of the patients showed such disturbances. All but 5 or 6 of the 50 patients presented some state of nervous tension, if one may use that term loosely, which seemed to have a relation to the intake of food. Most of these patients did not show what might be called an active or a clinically demonstrable psychoneurosis. When they were told by the physicians in the endocrine clinic that they should go to the psychiatric clinic, they remonstrated, saying, "I am not crazy; why do I have to go there?" When they came, they readily took an interest in the discussion of whether or not there was any relation between their nervousness, as we chose to call it, and their food intake. Again and again, the patient said "I am a nervous type; I feel better when I take food." In tracing the cause, we usually found one or another precipitating factor for anxiety. One group, which was not mentioned in the paper, was made up of a small number of patients who felt frustrated by life. "Why should I not eat? My husband comes home drunk every night. I can't stand him when he is that way. He never gives me money for any pleasure. So I eat. It is my only outlet." Such a patient is difficult to treat because there is not much that can be offered her. Other patients showed restlessness, with certain compulsive urges to partake of food. A psychiatric approach to the problem seemed to be of benefit. We feel that if the treatment of obesity is to succeed, most patients must have mental support. They must be kept under observation; otherwise they slip back into their old patterns. A few psychiatric interviews were helpful in a number of cases. In others lack of intelligence complicated the problem.

DR. H. D. PALMER: Another interesting phenomenon was the tremendous increase of weight noted in the patients with schizophrenia who had been subjected to frontal lobotomy. Such patients have lost anxiety and all nervous tension and show complete and utter relaxation. It would seem that in such a situation there is a release of inhibitory function which allows the patient to have a terrific appetite and to satisfy it. Five schizophrenic patients who had been underweight and who had undergone frontal lobotomy had an average gain of weight of 45 pounds (20.5 Kg.).

DR. ROBERT A. MATTHEWS: I don't know that I can answer the question as to why some patients who are anxious and tense lose weight and others gain, for there are certain problems yet not settled. The explanation may be related to the balance between energy intake and energy output and to body metabolism. In schizophrenic patients who gain weight after lobotomy there are a general quieting down and a flattening of the affect, as well as a blunting of social sensibility, which results in bad table manners and possibly in a tendency to eat too much. It is still not known why some people can eat a great deal and remain thin while others eat less and become fat. The physiologists will have to help with an explanation.

DR. J. C. YASKIN: I should like to get a clearer idea of the relation of anxiety states and the appetite. I have not seen patients with real anxiety who became fat. Except for the psychoneurotic patients who have a compulsion to eat, persons with anxiety states do not as a rule lose their anxiety with increased food intake. The patient with an involutional psychosis does not usually gain weight.

In questioning patients concerning possible conflicts responsible for their condition, one must follow the law laid down by Dunbar: It is not the presence of conflictual material that determines the production of symptoms but, rather, the reaction to that conflictual material. Any survey of large numbers of patients will give evidences of emotional conflict which may or may not be related to the symptom under scrutiny.

DR. ROBERT A. MATTHEWS: The tendency to read into something what is not there must always be guarded against. As a matter of fact, my colleagues and I asked ourselves whether we were suggesting possible factors to these patients and whether we were misinterpreting our observations or putting two things together which did not logically belong there. We tried to be as objective as possible. Perhaps we did sometimes put two things together which did not belong in the same category, but it was interesting to note how often the patient would produce material which seemed to represent his own observations on the relationship between nervous tension and eating habits. We did not see clearcut severe anxiety states in this group. I agree with Dr. Yaskin that patients with nervous tension do not as a rule gain weight unless there is a strong compulsion to eat. Compulsive tendencies were displayed by a good many of these patients.

DR. ROBERT R. SCHOPBACH: In a few cases, we found that gains in weight occurred soon after episodes which produced tension and that as tension was allayed the loss of weight followed the corresponding course. We thought that this indicated more than that the patient said he had tension and began to gain weight.

## Delayed Favorable Effects in Psychotherapy.

DR. JOSEPH C. YASKIN.

Delayed beneficial effects in psychotherapy are observed in five categories of patients: (1) psychoneurotic persons who at the time of treatment reject psychic factors as causes of their symptoms; (2) psychoneurotic persons who accept emotional factors as causes of their difficulties but whose progress in treatment is unsatisfactory; (3) patients under considerable external stress and strain; (4) patients with psychoneurotic conditions complicated by organic disease, and (5) patients with certain constitutional psychopathic states.

The causes of delay in improvement or recovery in these patients are related to the several mechanisms in psychotherapy. The fundamental process in psychotherapy is one of emotional equilibrium, whereas the intellectual component is usually of secondary importance. Even in the case of patients treated by the prolonged free association method the final insight is largely emotional. Successful psychotherapy begins with the acceptance on the part of the patient of the concept that emotional factors can produce physiologic disturbances and difficulties in adjustment. The technic of psychotherapy depends to a large extent on transference, which is an emotional relationship.

The patients who at the beginning reject psychic factors as causes of their disability, patients under considerable external stress and strain and patients with conplicating organic disease may terminate the initial psychotherapy with dissatisfaction, and even resentment, but later may have a change of attitude conducive to more satisfactory rapport, perhaps in the hands of another psychotherapeutist. The initial therapy, though rejected, often leaves a definite impression and acts as an "inoculation."

The patient who willingly accepts psychic causes but fails to make satisfactory progress by reason of the inherent difficulties of emotional exploration and equilibration often discontinues the treatment but nonetheless already has procured some vague feelings and formulations regarding psychologic mechanisms and often unwittingly continues a self analysis leading to a more satisfactory evaluation and a better adjustment.

### DISCUSSION

DR. K. E. APPEL: Dr. Yaskin has pointed out some interesting types of cases in which delayed favorable results of psychotherapy certainly appear. Many times we psychiatrists set the ball rolling and our patients go on to work out their problems themselves. We help them over acute stresses; and if they cannot continue therapy, they have to carry on their own treatment. A great many patients do so with reasonable effectiveness. I have even seen patients with psychoses who have been making pretty poor adjustments but who, when they break off therapy for some reason, have been able to carry on when they were thrown on their own and have got something out of their relationship with their physician. I should extend the group of patients which Dr. Yaskin mentions to include these.

I differ with Dr. Yaskin's statement as to the ineffectiveness of psychotherapy of the paranoid, manic-depressive and schizophrenic psychoses. There are certainly some patients who do not seem to be able to be touched by psychotherapy, but there are others, patients with paranoid conditions, schizophrenia and manic-depressive psychoses, whom I believe can be influenced by psychotherapy and can be helped, even independently of the drastic therapies.

I heartily agree with Dr. Yaskin in his emphasis on the emotional factors in psychotherapy. I believe that the processes of abreaction and of release are the most important tools in successful psychotherapy. I think that they are more important than intellectual understanding, intellectual formulations or the development of insight. It seems to me that many people live effectively and reasonably satisfactorily without the insight of normal people. If they are asked how they are living, or what they are living for, they cannot give a good account. The same is true of patients who recover from psychiatric disorders. Many recover without the development of insight; so it seems to me that insight is a condition which many normal people possess but which many normal people do not possess. It is also a condition which many patients acquire and many do not acquire, and I think that the striving for intellectual insight is a hindrance to effective psychotherapy.

DR. ROBERT A. MATTHEWS: Dr. Yaskin's paper should be reassuring, particularly to the young man who is starting out as a psychotherapeutist. He may feel frustrated when patients leave him and think that he accomplished nothing with therapy, but he may get delayed results.

DR. JOSEPH C. YASKIN: I want to call Dr. Appel's attention to the fact that psychotherapy was not useless in treatment of psychoses but was of limited value. We psychotherapeutists are helpful to our depressed patients. We encourage them and keep them as much as possible from attempting suicide. In a survey I made among my colleagues ten years ago concerning the prevention of recurrences of the manic-depressive psychosis, I did not get a satisfactory answer. We benefit people here and there, but a great deal more is to be accomplished. Six electric shock treatments do more for a patient with involutional melancholia than four years of psychotherapy. In my paper I have stressed the fact which Dr. Matthews has brought out, namely, that it is good not only for the younger men but for the men who are really doing the work, to be reassured.

**"Acting Out" as a Defense Mechanism: Report of a Case.** DR. GERALD H. J. PEARSON.

The analysis of an episode illustrating the mechanism of "acting out" was presented from the case history of a woman aged 28 who was suffering from major hysteria. While in the state hospital, she had barricaded herself in her room and then, with great effort, had secured three electric bulbs from the ceiling. She sat behind her bed with the three bulbs beside her. When the nurses broke into the room, she attacked them. At times during her analysis she imitated a dog and for long periods refused to stay on the couch, insisting on sitting on the floor close to the analyst.

These three forms of behavior were dramatic representations of the memories of her actions and feelings during her brother's birth, when she was 5 years old. When she first came for analysis, she had no conscious recollection of her mother's pregnancy, of her brother's birth, although she was in the house when it occurred, or of her brother as a baby. All of these memories were recovered during the analyses of the three forms of behavior just mentioned.

The case material illustrates that acting out is a frequently used mechanism whereby the recollection of memories of important childhood experiences is avoided.

DISCUSSION

DR. J. C. YASKIN: What was the final result in this case?

DR. GERALD H. J. PEARSON: The condition improved, but the patient is not completely well.

**Psychotherapy and Public Education.** Dr. O. SPURGEON ENGLISH.

Psychiatry has been receiving increasing publicity in the past few years, with good results. But it is felt that even more enlightenment of the public would be beneficial. Some of the ways in which such enlightenment has already been brought about are the public knowledge of selective service screening processes, the high rate of emotional casualties resulting from the war, books and articles dealing with psychiatry and more frequent allusions to the psychiatrist on the screen and on the stage, notably in the play and moving picture "Lady in the Dark." Inasmuch as the patient goes to the psychiatrist rather uninformed as to how the psychiatrist proceeds and uninformed about human personality in general, it seems important to utilize the various means of public enlightenment, such as newspapers, books, the radio, the stage and the screen, to make clear to the layman something of the nature of personality makeup. Why can it not become common knowledge that human beings are universally to some degree selfish, envious, sensitive, fearful, thoughtless and stubborn? Why not give more widespread exposition to the emotions of love and hate and how they occur, not to mention the frequency with which they occur? If the origin and existence of emotions such as these became more common knowledge, the patient going to a psychiatrist for help would not have to spend so much time in defending himself and protecting his self esteem. He and the psychiatrist would have a more common working knowledge of what produces emotional difficulties. Time would be saved in psychotherapy, not to mention the advantage of more effective and lasting results.

DISCUSSION

DR. A. H. PIERCE: All can agree with the theme of Dr. English's paper. In the past the interest of the public has been stimulated in regard to physical illness, and a great deal has been accomplished in educating it as to the character of this form of illness and the needs for preventing or escaping its ravages. Unfortunately, the public, perhaps like many psychiatrists, puts mental illness in an entirely separate category, although no one can deny that the human being is body and mind combined and inseparable.

Wars, deplorable as they are, seem always to be accompanied with tremendous advances. I do not hold that these advances counterbalance the ravages of war, but it is fortunate that out of the wreckage some good may come. After World War I great advances were achieved in the psychiatric field. The whole of psychiatry became revivified and was placed on something at least approaching a scientific basis. With this war there will undoubtedly come far greater advances.

Now and the postwar period is the appointed time for psychiatry to make itself heard and understood. I think that all psychiatrists are in agreement about this; the question is what means can be utilized in educating the public. As I see it, psychotherapy and mental hygiene are really parts of the same problem, although the former might be considered more prophylactic and the latter more exclusively therapeutic in character.

It is almost an axiom that before the public can be educated, it must first become interested. Today there can be no question of a very considerable interest, partly stimulated by selective service and Army discharges. If one wants proof of this it is furnished by the many articles in the lay press and the attendance at meetings dealing with problems of mental health to which the public are admitted. The lay attendance at the mental hygiene lectures now being given by the Philadelphia County Medical Society may be cited.

The public has today become aware of the existence of psychiatric problems and, to a lesser degree, of the means by which they can best be met. It is beginning to understand the "why" of emotional and mental disturbances. It is largely up to psychiatrists to show how these disturbances can still further be prevented or overcome.

DR. THOMAS WRIGHT: The Navy has made some good psychiatric moving pictures. Films such as these, if made available to the public, would do a great service to the cause of mental hygiene.

DR. S. B. HADDEN: It is my opinion that psychiatry is more than a therapeutic system. It is an educational discipline, and if we as psychiatrists accept the obligation to educate the public, a great deal can be accomplished. After all, psychiatry deals primarily with man's highest adjustment—his adjustment in the community. We can certainly indicate to the public that psychiatry has a contribution to make to humanity by teaching man how to live a fuller, more emotionally mature, existence.

DR. O. SPURGEON ENGLISH: I am delighted at the enthusiasm with which you have received these ideas. I trust that when the Chinese said, "One picture is worth a thousand words," their statement was meant to include a moving picture. The moving picture is a wonderful means of reaching a large group of people in a way that affects their emotions. The moving picture, the radio and the stage are probably the most vital means of informing the public of the therapeutic values inherent in psychiatric interviews. In

group psychotherapy, for instance, one of the factors that is known to be valuable is the patient's realization that he is not the only one who is having trouble with his feelings and his ideas. The office psychotherapeutic situation runs into the danger of becoming an isolated one, with the patient too likely to feel that he is the only one who suffers from his particular dilemma. If, through more public enlightenment, both patient and psychiatrist could allude to the current treatment of a human problem by the moving picture, the radio or the stage, their mutual task would be considerably easier.

## CHICAGO NEUROLOGICAL SOCIETY

ROBERT C. HAMILL, M.D., *President, in the Chair*

*Regular Meeting, Nov. 14, 1944*

**Traumatic Glossopharyngeal Neuralgia.** DR. HAROLD C. VORIS, Chicago, and (by invitation) LIEUTENANT J. T. BAKODY, MC (V), U.S.N.R.

In June 1944 a Marine sergeant aged 23 was injured in combat by mortar shell fragments. One fragment entered below the left external ear, just anterior to the mastoid process, traversed the structures of the neck in the lateropharyngeal space and entered the pharynx through the tonsil. The patient actually spit out the shell fragment from his mouth. There was considerable bleeding but no loss of consciousness. He stated that there was immediate paralysis of the left side of the face and that after the injury intermittent pain developed on that side of the face, which has persisted up to the present time. Swallowing, chewing, coughing and sneezing precipitate the attacks of paroxysmal pain. The pain seems to begin at the left malar eminence and radiates into the left eye and left ear; it is severe and lancinating and lasts twenty to thirty seconds. An apparent autonomic concomitant, with unilateral flushing of the lower part of the face, has been observed. More recently the pain in the ear has become more prominent, with prickling sensations deep within the ear.

The physical findings are essentially normal except for those referable to the left side of the head. There is a healed shrapnel wound of entrance just below the lobule of the left ear, while the wound of exit is a small opening, about 1 cm. in diameter, at the anterosuperior pole of the left tonsillar fossa. Partial tonsillectomy has been accomplished by the shrapnel in this area. Stimulation of the left tonsillar region with an applicator reproduces the characteristic pain. On the other hand, cocainization of the left tonsillar area abolishes the trigger zone, and the pain cannot be reproduced while the cocaine is effective. The tenth, eleventh and twelfth cranial nerves are apparently normal. There is slight residual paresis of the lower left side of the face of peripheral type. Roentgenographic studies are normal for the skull, the mastoid region and the left styloid process.

DISCUSSION

DR. HAROLD C. VORIS: The radiation of this patient's pain, as described, is not exactly typical of that described as glossopharyngeal neuralgia. However, the abolition of the trigger area is quite characteristic. Neuralgia of the fifth cranial nerve is much more common than glossopharyngeal neuralgia. Traumatic injury of the fifth nerve is also relatively common. As a matter of fact, the supraorbital branch of the fifth nerve is the most frequently injured cranial nerve because of the frequency of supraorbital laceration. Injury of the maxillary nerve is usually the result of injury to the facial bones. The maxillary nerve may be injured in cases of fracture of the maxilla. Likewise, injury of the mandibular nerve is more frequent with fractures of the mandible than with injuries to the base of the skull. However, both these nerves may be injured in connection with basal skull fracture.

I had a patient with a basal skull fracture who was operated on for a hemorrhage of the middle meningeal artery. When he regained consciousness, he had anesthesia of the mandibular nerve, which was persistent. I have seen only 2 cases of paroxysmal facial pain (both in the maxillary distribution) in which the picture conformed to the classic syndrome of trigeminal neuralgia and seemed to bear a definite relationship to a previous basal skull fracture. Both patients had onset of pain within six to twelve weeks after injury, and both were relieved, temporarily, by injection of alcohol into the maxillary nerve. I did not see them again and do not know whether the pain recurred, as is always the case with true trigeminal neuralgia. Certainly, there is an unusual combination of circumstances in this case—first, the isolated injury to the glossopharyngeal nerve and, second, the prompt appearance after the injury of neuralgia, which I believe is true glossopharyngeal neuralgia.

DR. PETER BASSOE: I understand this patient had some redness of the face, and I should like to ask whether he noticed that his face perspired and became red after eating. If so, one might think that the auriculotemporal nerve was involved. This injury is often associated with facial palsy and involvement of other nerves to the face. The patient says he did not; so that settles it.

DR. R. P. MACKAY: I should like to ask whether the trigger zone was definitely located. It is insufficient to say that coughing, sneezing or swallowing produced the pain, for these activities stimulate wide areas in the mouth, extending far beyond the area innervated by the glossopharyngeal nerve.

DR. HAROLD C. VORIS: When I saw this patient, he had had the tonsillar fossa cocainized that morning and had been able to eat lunch comfortably. During the period of anesthesia of the trigger area it had been demonstrated that stimulation of that area did not produce pain. At the time of my examination the effects of the cocaine had worn off, and stimulation of the tonsillar fossa produced the usual paroxysm of pain.

I presume the nerve injury is in the retropharyngeal space. I was asked whether section of the glossopharyngeal nerve in the neck was advisable. I stated that an attempt at exploration in the neck, because of the possibility that the injury and resultant scar involved the great vessels, might be more dangerous than cranial section of the nerve. Moreover, peripheral section of the nerve cannot be expected to give permanent relief, while cranial section will do so.

**Effects of Penicillin on the Central Nervous System.** DR. HERBERT C. JOHNSON, DR. A. EARL WALKER and DR. THEODORE J. CASE.

DISCUSSION

DR. CLARENCE NEYMANN: Through the Commercial Solvents Corporation, Dr. Heilbrunn and I were presented with a large amount of penicillin for experi-

mental purposes. We have used this drug in treatment of patients with far advanced dementia paralytica at the Chicago State Hospital. At first the drug was administered intravenously and intramuscularly. Later it was injected intracisternally. Five patients were treated with approximately ten daily intrathecal injections of penicillin. The first patient, who was given too great a dose (100,000 units) exhibited a state similar to that shown in the moving picture of the cat. After an initial period of severe headaches and restlessness, there developed tenseness and muscular twitching, ending in generalized convulsions. His life was saved with some difficulty by placing him in an oxygen tent and quieting him with sodium amytal and morphine. After twenty-four hours he recovered.

The purity of the drug seems to influence the reaction. In the beginning any dose above 30,000 Oxford units of penicillin of 25 per cent purity given daily produced tenseness, twitchings and, finally, convulsions. At present we are giving up to 40,000 units of penicillin of 40 per cent purity without serious complications. We have been promised crystalline penicillin; this may solve the problem. It seems that there is some relation between the amount of the impurities and the severity of the reaction.

As in the animal experiments, the cell count of the spinal fluid in man rises abruptly; red blood cells appear in the spinal fluid, together with polymorphonuclear cells and lymphocytes. We are not prepared to say whether the patients will benefit from this therapy. However, the colloidal gold curve has shown a tendency to flatten out to normal. The penicillin disappears from the spinal fluid in twenty-four hours. No penicillin enters the spinal fluid if the drug is injected intravenously or intramuscularly, even in huge quantities. With the intrathecal method of administration we have noted no convulsions or other serious complications. Therefore the purity of the product used experimentally by the authors is of great interest.

**Extradural Hemorrhage: Report of a Case.** DR. A. VERBRUGGHEN.

A man aged 75 was admitted to the hospital six hours after falling 4 or 5 feet (1.2 or 1.5 meters) onto his buttocks. He rose, walked to the house, climbed fourteen steps, sat down on a chair and during the course of the next half-hour lost complete control of his legs. This paralysis was associated with excruciating pain in the arms and back and with numbness from the nipple line downward. He was examined six hours later, when he showed complete paraplegia with loss of sensation below the nipple lines, absence of reflexes, a bilateral Babinski sign and urinary retention. There was an uncertain sensory level at the seventh or eighth cervical segment on the hand. There were movement in the upper extremities, weak extension and fairly strong flexion. The biceps reflexes were present bilaterally, but the triceps reflexes were not obtained. Spinal puncture could not be carried out because of long-standing arthritis of the spine of Marie-Strumpell type. Roentgenograms of the cervical portion of the spine did not reveal any fracture dislocation.

Because of the history of progressive symptoms, operation was immediately undertaken; beneath the fifth and the sixth and part of the seventh cervical lamina was found an extradural clot, measuring 5 by 2 by 1 cm. When this was removed, the dura pulsated freely. The wound was closed rapidly, and the patient was sent back to bed. The following day the level had descended to the tenth thoracic segment, and there were very faint movements in the legs. By the third postoperative day the sensory level had descended to the knees, and there were more powerful movements in the legs. By the fourth postoperative day sensation to pinprick was restored over the entire body, and all muscular movements could be performed in the legs, although they were weak. During the course of the next ten days the patient regained ability to void and the catheter was removed; he was sent home, where he made an uninterrupted recovery. The case is reported because of its rarity. A review of the literature reveals little convincing evidence of similar cases. In the cases reported the hemorrhages were either traumatic or spontaneous.

DISCUSSION

DR. VICTOR E. GONDA: An extradural hemorrhage would have to be fairly large and hard to press on the dense dura mater and compress the spinal cord completely. The question arises whether early evacuation of the blood in a case of suspected extradural hemorrhage would not prevent serious and irreparable damage.

DR. J. P. REICH: I remember a case in Breslau, Germany, many years ago. A young boy, while playing the piano, suddenly had a terrific pain in the back. A physician, who was immediately called, found flaccid paralysis of both legs. When a neurologist arrived, after a short time, the paraplegia had disappeared completely. The diagnosis of epidural hemorrhage was made, and the rapid disappearance of the motor disturbance was explained by the flowing of the blood down into the lowest part of the dural sac. According to a personal communication which I received from a co-worker of Prof. Otfried Foerster, it is possible in such cases to remove the blood by a needle introduced into the sacral portion of the canal.

DR. A. VERBRUGGHEN: With regard to Dr. Reich's comment, I do not understand how hemorrhage could occur in the cervical region and the blood be removed by inserting a needle into the sacral hiatus. It is difficult to understand how one could be sure that there was blood to be found or why it would track down from the cervical to the sacral region or why, if it did, it should be removed.

I do not believe that Dr. Gonda is suggesting that all patients with injuries to the spinal cord should be operated on at once for fear there might be an extradural hemorrhage; extradural hemorrhage is an extremely rare condition, and this is the first case I have seen in fifteen years of neurosurgical practice. The mechanism is probably that of pressure on the spinal cord produced in much the same way as pressure from extradural hemorrhage is exerted on the brain. The coagulation of the blood probably causes some reaction in the spinal cord. In this case spinal shock was present, though the paralysis came on slowly. There is no remedy for this mechanical compression of the spinal cord except mechanical removal. The picture would be further complicated if, in addition to a fracture dislocation which was not causing compression of the cord, an extradural hemorrhage occurred which did cause compression of the cord; in such a case, however, the progressiveness of the symptoms would be of the utmost importance.

In the case of traumatic hemorrhage described by Jonas there was no fracture dislocation, but the surgeon

merely operated at the level indicated by the sensory level. However, in 2 other cases described in the literature it was apparent that the hemorrhage was spontaneous. One cannot be sure from perusal of the history, of course, whether a careful postmortem examination was made or not. In 1 instance, however, an 18 year old housemaid had had difficulty at stool in the morning. Half an hour later she experienced great pain in her arms. In two hours she had complete paralysis of the upper and lower extremities, and in two hours and a half she died of respiratory failure, with an extradural hemorrhage beneath the second and third cervical vertebrae. In another case a man, while shoveling snow, experienced a wrenching of his back and over the period of the next twenty minutes felt weakness in the legs. During the course of the next twenty-four hours one leg recovered, but the other was still paralyzed; in the meantime he had urinary retention, and he finally died on the fourth day after this spontaneous injury. In this case an extradural hemorrhage was found in the lumbar region of the spinal cord. In the case of the young woman the pathologist stated that he had rarely examined more healthy organs. The question whether any of these patients may have had hemophilia was not entered into.

Archives of Neurology and Psychiatry

VOLUME 54 SEPTEMBER 1945 NUMBER 3



# STUDIES ON CEREBRAL EDEMA

## I. REACTION OF THE BRAIN TO AIR EXPOSURE; PATHOLOGIC CHANGES

M. PRADOS, M.D.; B. STROWGER, M.A., AND W. H. FEINDEL, M.Sc., M.D.
MONTREAL, CANADA

It has been observed by neurosurgeons that in a certain number of patients undergoing large craniotomies involving exposure of the brain for long periods and cortical exploration there develop focal symptoms of paralysis, such as hemiplegia and aphasia, even when no cerebral substance has been removed. These symptoms appear within a few hours or one to two days after operation and are generally transitory, although they may persist in some cases for several weeks.

At Dr. Penfield's suggestion, Echlin[1] started a series of experiments to determine what effects on the brain or the meninges might be produced by operative exposure. He described lesions following simple exposure of the brain at operation which, from their nature and the similarity of their anatomic distribution to those produced by electrical stimulation, appeared to him to be due to cerebral ischemia. In those animals whose brains were exposed at operation for more than one hour he described adhesions between the leptomeninges and the pachymeninges, which appeared as early as the third postoperative day but when the dura was opened and immediately closed again, such adhesions did not occur except under the dura in the region of the silk sutures. He described also an inflammatory reaction in the leptomeninges, which disappeared eight days after operation. He found triangular areas of gliosis in the cat brains that had been exposed to air for two hours; the lesions were not prevented by protecting the brain from dry air with a glass covering or by irrigating continuously with solution of three chlorides U. S. P. at body temperature. He expressed belief that the gliosis was the result of a relative ischemia of the gray matter caused by compression of the pial blood vessels, which possibly was produced by the inflammatory exudate and adhesions that were shown to follow operative exposure of the brain.

From the Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute.

1. Echlin, F. A.: Cerebral Ischaemia and Its Relation to Epilepsy, Thesis, Faculty of Graduated Studies and Research, McGill University, 1939, p. 39.

Echlin's paper is interesting inasmuch as he attempts to give an explanation on an experimental basis of the aforementioned clinical findings. His conclusions are interesting enough to justify further investigation. We have repeated Echlin's experiments with a large series of animals and have followed closely the chronologic sequence of the cerebral reaction from the physiologic and the pathologic viewpoint.

In the present article we shall describe the pathologic observations made during and after the exposure, and in later papers we shall discuss the various physiologic changes.

### MATERIAL AND METHODS

Cats were used in all our experiments. Aseptic technic was followed in all the exposure experiments. Anesthesia was obtained by the intraperitoneal injection of 0.6 grain (0.039 Gm.) of pentobarbital sodium per kilogram of body weight of the animal. A cranial incision was made in the midline, and the left temporal muscle was removed partially from its origin. An opening was made in the skull with a trephine and enlarged with rongeurs until it was approximately ¾ inch (1.9 cm.) in length and ½ inch (1.27 cm.) in width. The dura was gently lifted with a small curved needle and punctured with a small scalpel. A grooved director was gently inserted through the slit, and the mesial, the anterior and the posterior edge were cut. The dura was then carefully reflected laterally so that the brain was exposed in an area a little smaller than the size of the opening in the skull. The exposed area of the brain extended from the lateral sulcus down to the suprasylvian and middle ectosylvian gyri. The length of the exposure varied from four to seven hours. The dura was then closed with two silk sutures at each free corner. The galea and the muscle were then closed carefully. Sulfadiazine powder was placed on the suture and a small dressing applied to the wound; it was held there by means of liquid adhesive. The animals were killed by bleeding while they were under pentobarbital sodium anesthesia or with an overdose of pentobarbital sodium. They were killed immediately after exposure or at intervals of one, two, three, five and six days. In some cases solution of formaldehyde U.S.P., diluted 1:10, was injected into the brain after perfusion with isotonic solution of sodium chloride. The brains were fixed in formal solution of formaldehyde U. S. P., diluted 1:10, or in ammonium bromide-solution of formaldehyde or in alcohol. Blocks were cut on the freezing microtome or after embedding in paraffin or pyroxylin. The gold chloride (modified) method was used for astrocytes, and modifications of the Hortega silver carbonate technic, for oligodendroglial and microglial cells. Thionin and cresyl violet stains were used

for neurons in paraffin or pyroxylin sections. The hematoxylin-eosin stain or the Van Gieson and Weil method for myelin were also employed. The benzidine method was used for the vascular network.

## RESULTS

Immediately after the opening of the dura the brain showed pulsating movements, which followed the respiratory rhythm. These movements stopped generally about two hours after exposure. At that time a certian degree of swelling of the brain substance was usually observed, as revealed by the bulging of the exposed area through the bone wound. The degree of swelling varied a great deal from one experiment to the other, and it depended on some factor the nature of which we are not yet able to determine. This swelling might reach such a degree as to make the closing of the dura impossible; a subsequent herniation, with injury of the brain substance, might take place. But as a rule the swelling was moderate and allowed the closing of the dura, although the edges could be brought into contact in only a few cases.

*Vascular Changes.*—Changes in the circulation were conspicuous a short time after the exposure. It is interesting to follow them in their chronologic sequence because they are of importance in explaining other functional and structural changes in the brain following the exposure.

As Echlin described, the meningeal vessels began to dilate about half an hour after the dura had been opened and the brain exposed. Dilatation was first seen in the veins, and for a while passive congestion was evident. This dilatation of the vessels gradually advanced until, by one and a half to two hours after the exposure, arteries as well as veins were dilated,

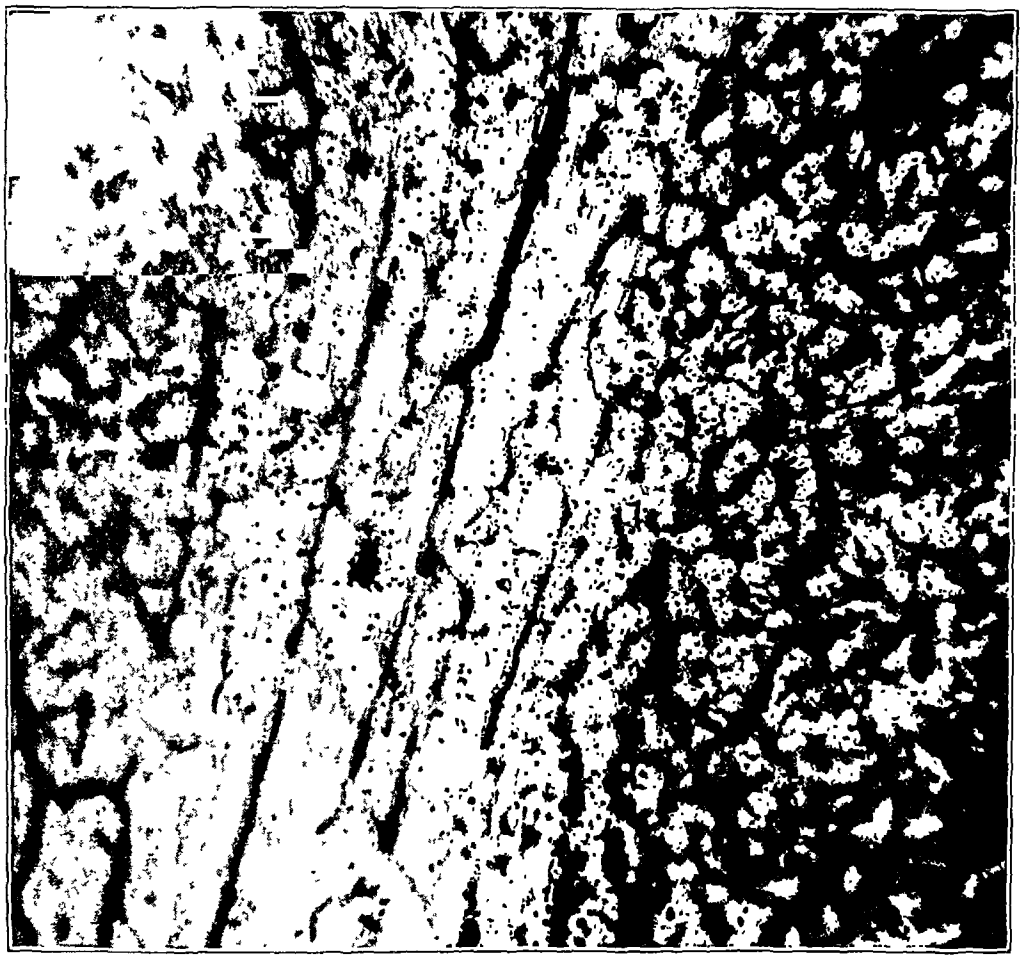


Fig. 1.—Diapedetic hemorrhages in the brain twelve hours after exposure. Benzidine stain.

engorged and prominent, and many vessels which were not visible to the naked eye became so during the exposure, the whole exposed area showing a diffuse pinkish blush.

Postmortem examination of the brain at this time showed that this vasodilatation, although much more prominent over the exposed area of the brain, extended over the entire brain, including the vessels of the diencephalon. In coronal sections of the brain one could see numerous red cells in the subarachnoid spaces and in the ventricles, mainly the third, and in the infundibulum. On microscopic examina-

tion of the brain stained by the benzidine method definite engorgement of the large vessels was found, more prominent in the veins than in the arteries. Under a low power lens, one noticed a very irregular distribution of the blood in the capillary network and patches of empty or collapsed capillaries, especialy around the large vessels. Small perivascular hemorrhages could be found through the whole brain, in the gray as well as in the white matter (fig. 1), along the periventricular region, in the periventricular gray matter of the third ventricle and in the

Fig. 2.—Capillaries of the white matter of the brain twenty-four hours after exposure. Benzidine stain.

tuber cinereum, where the vessels seemed to dilate and become engorged to a conspicuous degree. Capillaries (fig. 2) and small vessels showed either dilatation and stasis or were empty and irregular in shape. Many of these vessels showed the formation of slight bulging or small aneurysm-like widenings, which indicated loss of tonicity of the wall. In most of the cases the hemorrhages were only diapedetic. Real hemorrhages, with loss of continuity of the wall of the vessel, were rare and were consistently present only when the swelling was pronounced and herniation of brain substance took place. In these cases large hemorrhages could be found in the exposed area and its vicinity and were conspicuous in the white matter.

If the animal was killed twenty-four hours after the exposure, the picture changed somewhat (fig. 3). The meningeal vessels were still engorged with blood. The brain, however, in many places showed definite signs of ischemia. Many arteries were dilated and distended and contained little or no blood, but the veins still showed stagnation and irregular dilatations to a considerable degree, especially in the deepest layers of the gray matter and in the white matter, where the venous stagnation seemed to be at its height. Extravasated red blood cells had mostly disappeared and could be seen only in places where the hemorrhages were larger. The perivascular spaces were now very wide. Many of the capillaries were collapsed. The nuclei of the endothelium were pyknotic, and the protoplasm of the cells might show vacuolation. Occasionally small vessels or capillaries exhibited dilatations, filled with red blood cells. Rarely, however, the endothelium showed actual breaks, although in a few isolated instances one could even see retractions of the vessels at both ends and accumulation of blood cells in the perivascular space.

On the third day the ischemic patches of the cortex began to be less evident, and the normal circulation seemed to be reestablished. Dilatations of the veins and of some arteries still persisted, especially in the deep layers of the gray matter and in the white matter, showing that their walls had been damaged somewhat and had lost their tonicity.

On the fifth day after the exposure (fig. 4) benzidine staining of the brain showed a normal picture except for a few bulges or aneurysm-like widenings of some vessels. The perivascular spaces had come back to their normal appearance.

*Cellular Changes.*—Two types of neuronal changes were observed: (*a*) swelling and chromatolysis, and (*b*) shrinkage and homogenization. Although these alterations correspond with the classic descriptions made by histopathologists, we prefer to describe them as they were found in our slides.

Swelling and Chromatolysis: In the swollen cells (fig. 5) the protoplasm was lightly stained, and its processes were swollen and not clearly seen; many of these cells, however, did not show any processes at all and were round or irregular in shape. The cytoplasm of the cell body might show numerous vacuoles, which gave it a sponge-

like appearance. The substance was completely absent or was diffuse, dustlike and generally displaced to the periphery. The nucleus was large and swollen, with little or no chromatin; it was displaced in many instances to the periphery but frequently occupied almost entirely the whole cell body, occasionally being partially surrounded by a small zone of deeply stained cytoplasm. The nucleus in most cases was perfectly round, but in many instances the nuclear membrane was shrunken and the nucleus irregular in shape. The vacuoles in the cytoplasm seemed to push the nucleus in many directions, contributing to its irregular form. The nucleolus was large, rounded and deeply stained. In some cases the cellular membrane seemed to have burst, and no protoplasm was seen around the nucleus, which appeared to be the only remaining cellular structure. In other instances, a very pale, unstained silhouette or irregular outline, without any structure, was all that remained of the cell.

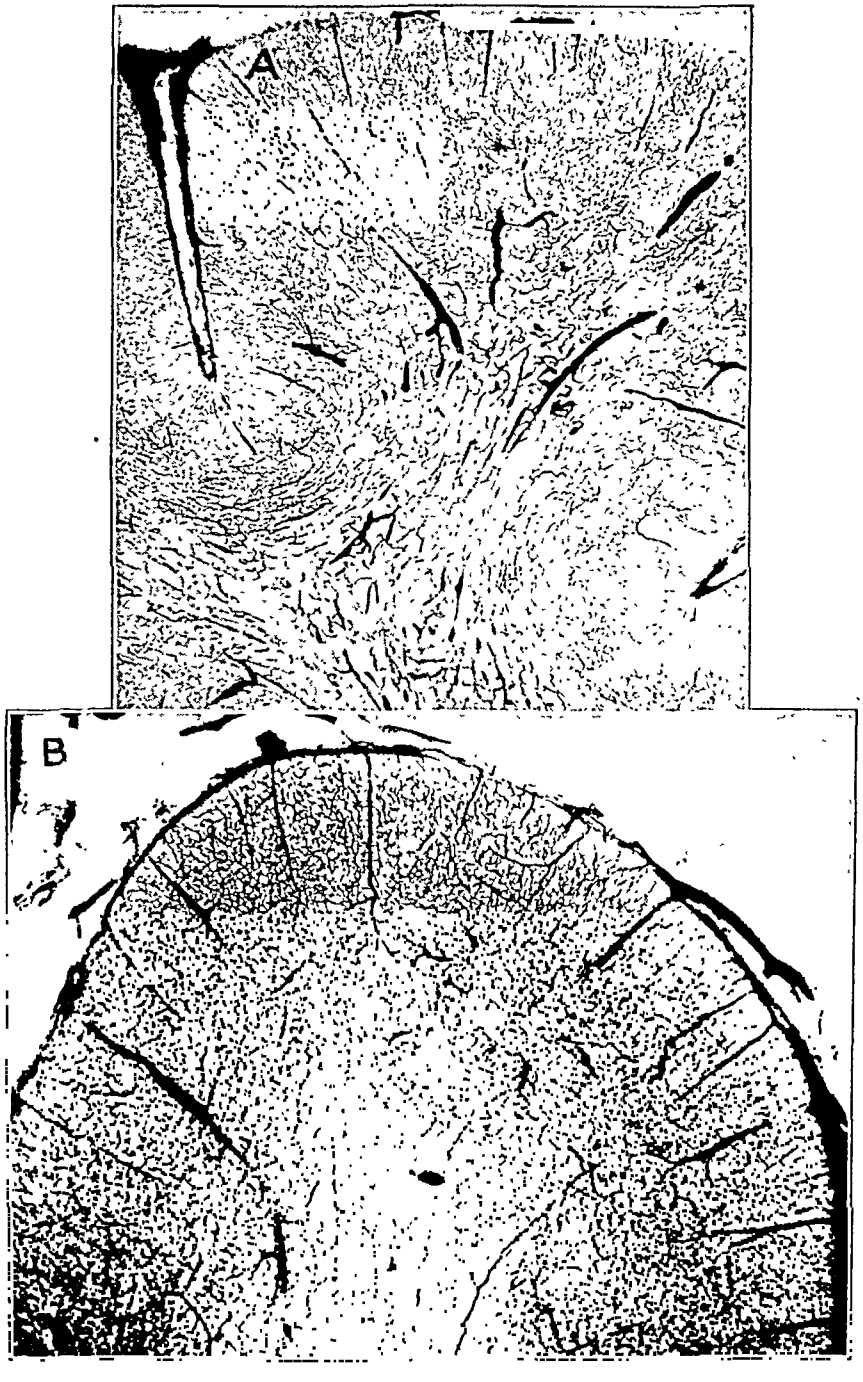



Fig. 3.—*A*, cerebral cortex, showing ischemia of the gray matter and engorgement of the deep vessels twenty-four hours after exposure. *B*, normal cerebral cortex of the cat. Benzidine stain.

Shrinkage and Homogenization (fig. 6): The neurons were shrunken and darkly stained, with angular corners; concave depressions appeared in the sides of the cell body, the shrinkage affecting only the diameter of the cell, and not its length. In fact, the cell might actually show

an extraordinary degree of elongation. The pale-stained processes were wavy and crinkled and could be followed for some distance from the cell body. Only the cell body was dark. The nucleus was irregular in shape and usually elongated, like the cell body, its outline not being very clear. A dark-stained nucleolus could almost always be seen, and usually quite in the center of the nucleus. The cytoplasm was stained homogeneously dark blue (thionin), although darker masses could be seen sometimes around the nucleus, making difficult the determination of its outline. These dark masses stopped sharply at the origin of the processes, which remained lightly stained. With the silver carbonate method, the same picture could be seen, although the cytoplasm was uniform and pale, and the nucleus, which was sharply seen, was very dark.

The degree to which these cellular alterations appeared in the brain seemed to depend on the length of time which had elapsed since the exposure. Immediately after the exposure swelling and chromatolysis predominated. This cellular change was still frequently seen during the next twenty-four hours, although by that time, when the benzidine method revealed prominent patches of ischemia, the shrinkage and homogenization were more in evidence.

These neuronal alterations were not exclusively localized to the exposed area. Indeed, they could be seen as well in both hemispheres throughout the whole brain, including the subcortical structures at the base of the brain. They were, however, more conspicuous in the more caudal and ventral regions of the cortex, chiefly in the lobus pyriformis, the occipital pole and the cornu ammonis. The lobus pyriformis on each side was without any doubt the region that showed the largest number of altered cells.

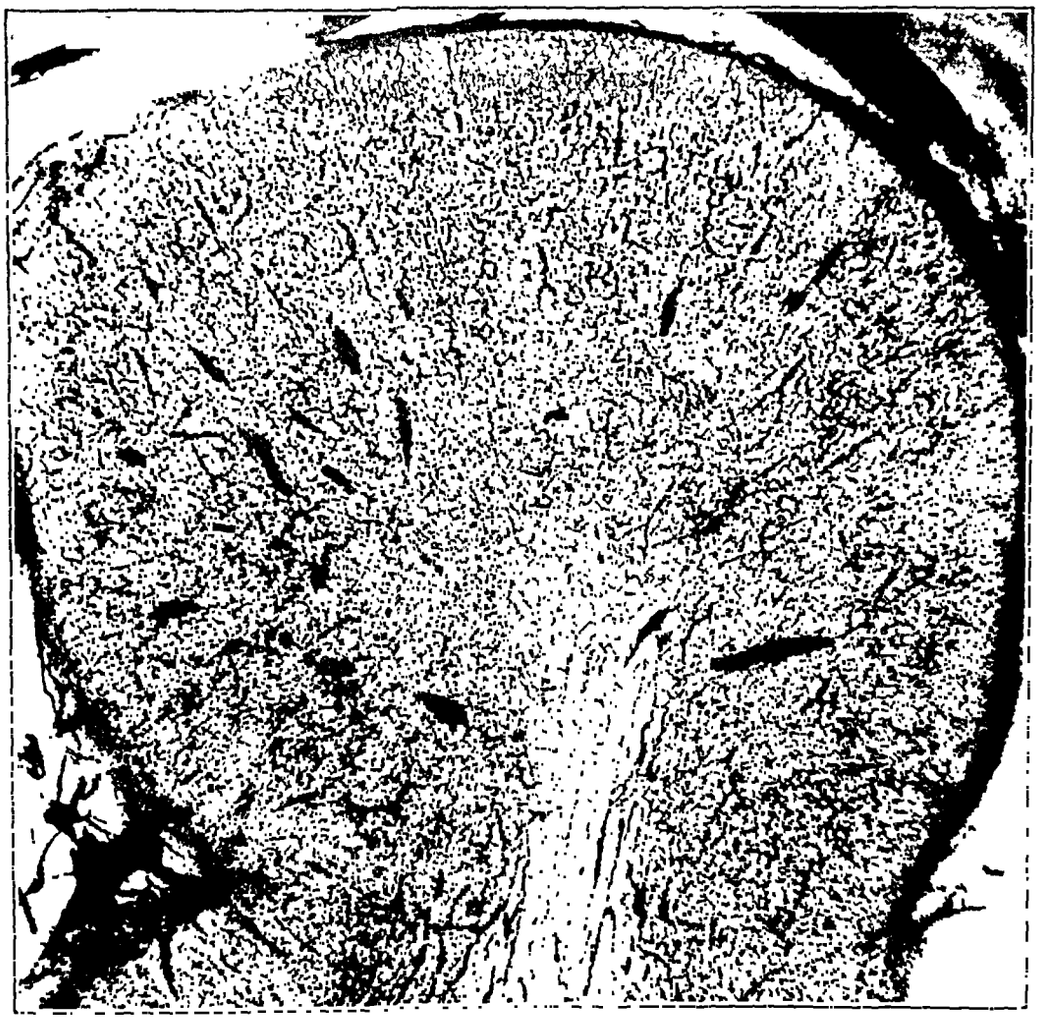


Fig. 4.—Cerebral cortex five days after exposure, showing reestablishment of the circulation. Dilatation of some deep vessels still remains. Benzidine stain.

Swollen cells became rarer twenty-four hours after exposure, and shrunken, homogeneous cells dominated the picture. Zones or areas of devastation could already be seen, indicating that some of these swollen cells had undergone complete disintegration. However, many swollen cells could still be seen in the deeper layers of the cortex, whereas in the more superficial layers most of the cells showed shrinkage and homogenization. Forty-eight hours after exposure the latter alteration was the only type found, chromatolysis and swelling no longer being present. At this time the histologic picture of the cortex was characteristic (fig. 7). The larger vessels

were still engorged and filled with blood cells. The perivascular spaces of both large and small vessels were prominent and very wide, as were the perineuronal spaces of the shrunken neurons. A few swollen cells and zones of devastation completed this picture of a mild but evident edema-like condition. By the third and fourth days the histologic picture began to return to

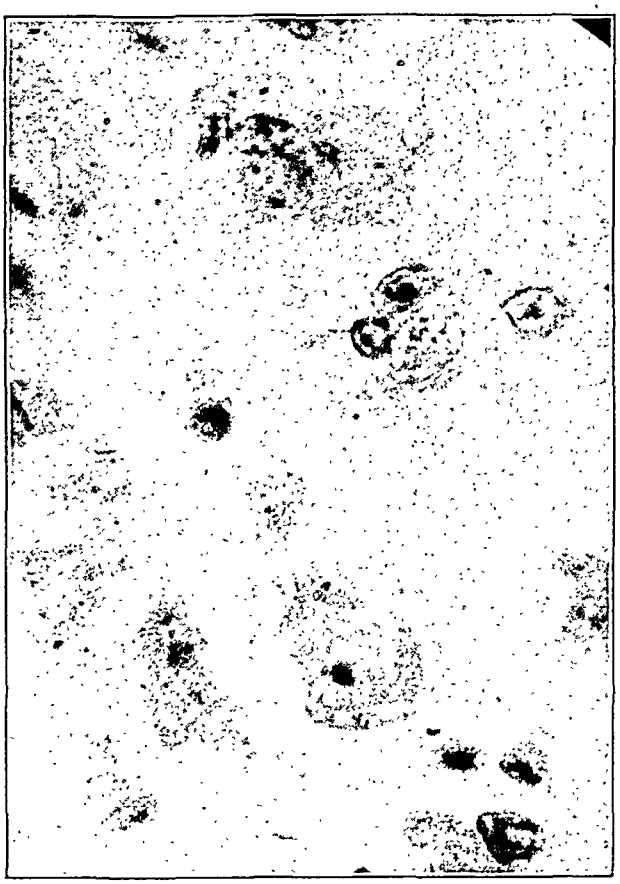


Fig. 5.—Neurons of the cerebral cortex, showing acute cellular alteration. (See text.) Nissl stain.

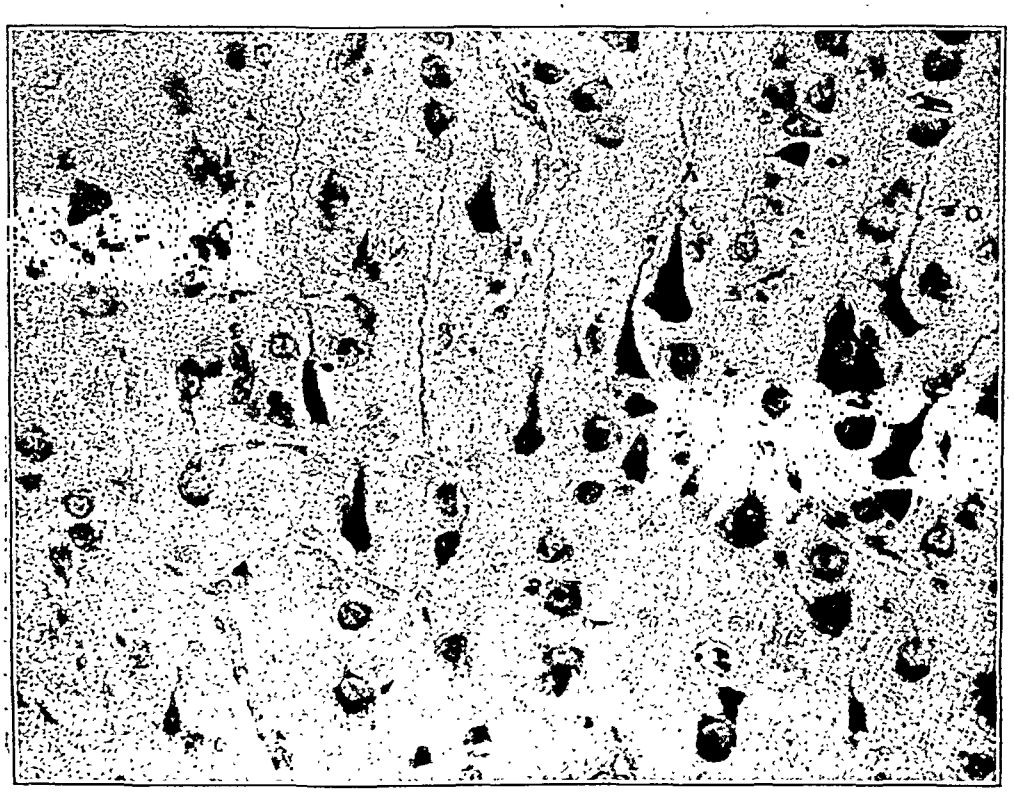


Fig. 6.—Cerebral cortex, showing different types of neuronal alterations following exposure (for twenty-four hours). (See text.) Nissl stain.

normal in most of the regions of the brain except the lobus pyriformis, which still showed the shrunken neurons. Isolated small groups of shrunken cells might be found, however, for a few days, but they were no more frequent than was usually seen in the control animals.

*Interstitial Cells.*—Of the three types of interstitial cells, only the oligodendroglia cells remained completely normal. Astrocytes and microglia cells showed changes of varying kind and degree, according to the length of time after the exposure.

As might be expected, the cells that showed the earliest changes were the microglia cells (fig. 8); indeed, such changes appeared within twenty-four to forty-eight hours after the exposure. Although microglial cells react rapidly and with moderate intensity, this reaction was temporary. Both progressive and regressive changes were seen simultaneously. There was an increase in size which affected both the processes and the cell body; the dendrites were thick, with sharp contour, beset with spines and of angular outline; the delicate small branches had disappeared, so that the cells exhibited only their more primary branches. Cells adopting the so-called rod shape, as well as elongated cells, were seen, although the former were very scarce. The cell body appeared swollen and showed a coarse reticulated structure. The nucleus was small, pyknotic and displaced; granules of different sizes and shapes at times occupied almost the whole body. In a later stage the processes became thinner and broke up, whereas the cell body continued to swell, until finally it might "explode." Compound granular corpuscles, however, were never seen, but a certain mobilization of the affected cells was present, as demonstrated by the fact that around the vessels, and even in their perivascular spaces, were cells which seemed to discharge their stored granules into the capillaries. After the fourth day, however, microglial cells might show slight changes in isolated areas but for the most part were entirely normal.

*Astrocytes.*—Little or no change was seen in the neuroglia during the first days after the exposure. In some cases, however, it seemed that the exposed area of the cortex showed hyperplasia of both types of astrocytes, which was more marked in the supragranular layer and in the marginal neuroglia. Later, about the fifth or the seventh day, a true gliosis might appear. Not only was there an increase in the number of gliocytes, but hypertrophy of both body and processes might be present. No protoplasmic neuroglial cells were seen, all being of the fibrous type, with very thick processes. As Echlin showed, this gliosis was particularly noticeable in the marginal neuroglia of the exposed area but invaded as well most of the gray matter and even the underlying white matter. It may be interesting to point out that acute regressive changes were never seen at any moment, even on the first day after the exposure. The changes observed were only pro-

Fig. 7.—Exposed cerebral cortex, showing edema reaction. Low power; Van Gieson stain.

gressive in nature and were certainly reactive to circulatory alterations.

*Blood-Brain Barrier.*—The histologic picture already described showed us clearly that as a result of the exposure to the air of a limited area of the cat brain there develops a generalized reaction of the whole brain, which disappears almost completely after six to seven days. This reaction affects primarily the vessels, with the result that there is an increase in the outflow of fluid from the vessels into the tissue spaces. The numerous diapedetic hemorrhages and the bulging and aneurysm-like dilatations of capillaries show that the permeability and tonicity of the capillary endothelium are altered.

In order to ascertain to what extent the permeability of the blood-brain barrier was affected during the exposure, the behavior of solutions of trypan dyes on intravital injection was observed.

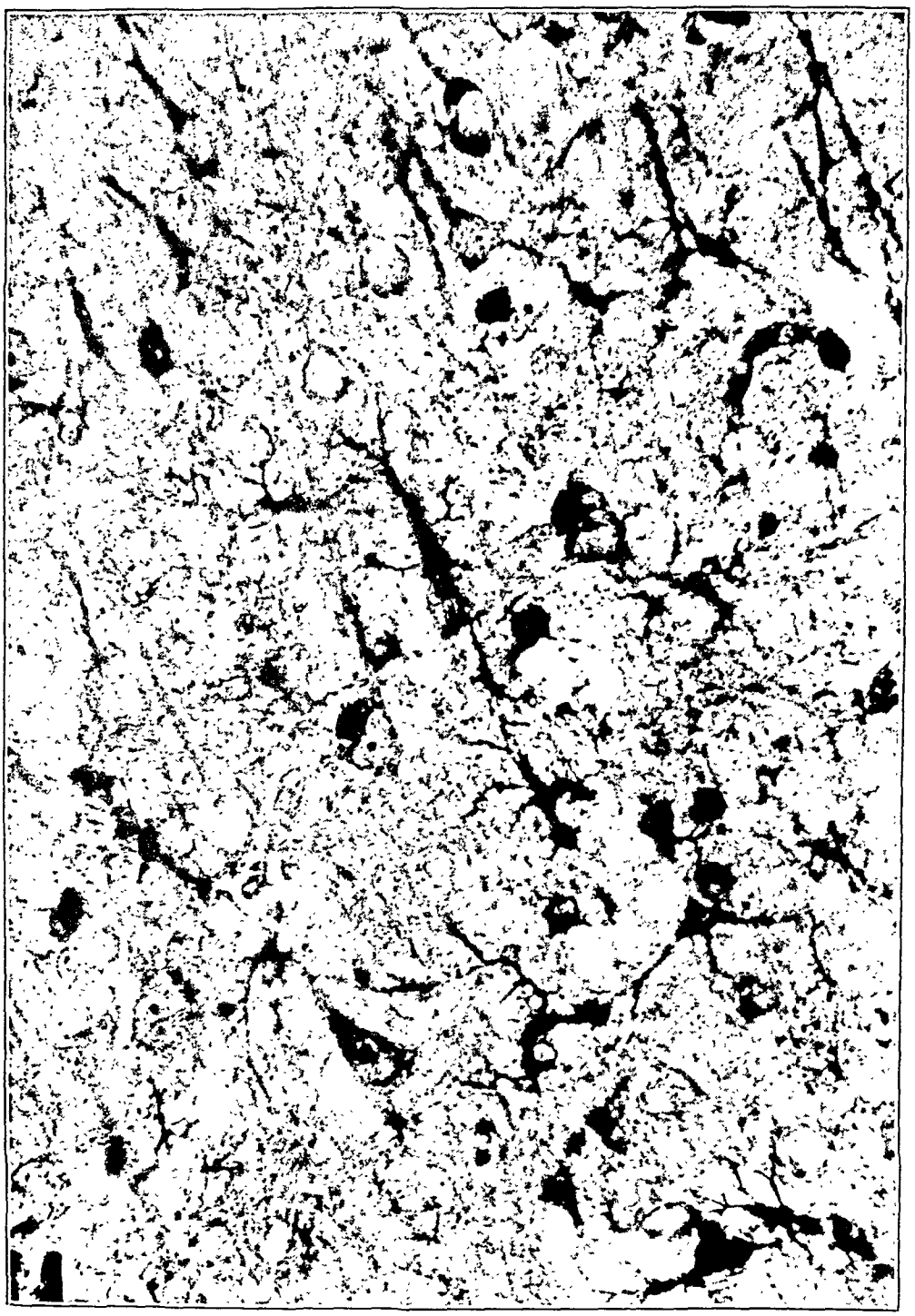


Fig. 8.—Slight microglial reaction twenty-four hours after exposure. Silver carbonate stain.

Goldmann [2] first demonstrated the fact that solutions of trypan blue, when injected into experimental animals, stain all organs of the

2. Goldmann, E. E.: Vitalfärbung am Zentralnervensystem, Berlin, G. Reimer, 1913.

body diffusely except the leptomeninges and the brain, which remain "snow white," to use the expression of the aforementioned investigator. Only limited and specific structures of the brain are stained, i. e., the chiasmic region, the tuber cinereum and pituitary body, the choroid plexuses and the area postrema. These experiments, widely confirmed later by numerous investigators, gave clear evidence for the first time of the presence of what has since been called the blood-brain barrier. This implies that the permeability of the endothelium of the capillaries of the brain is more selective than that of the capillaries of most other organs, at least for certain kinds of colloidal solutions, such as the trypan dyes.

From 10 to 20 cc. of a 1 per cent aqueous solution of the dye was injected into our animals at the end of the exposure. The injection was

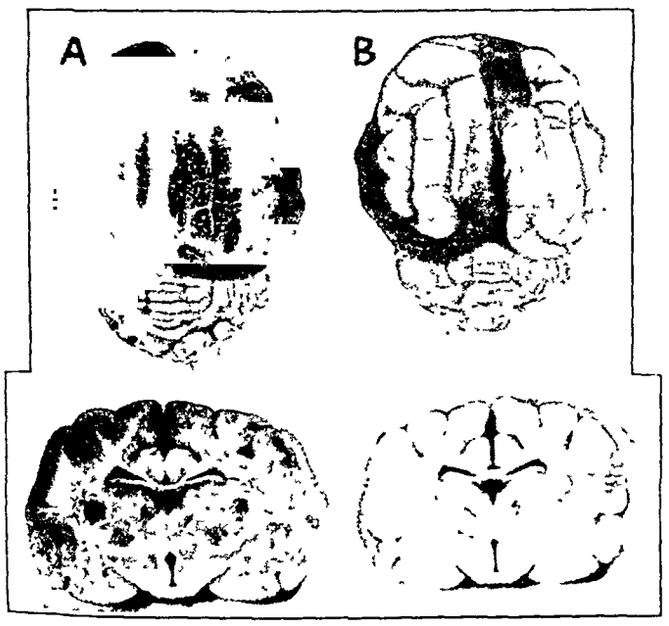



Fig. 9.—Increased permeability of the cerebral capillaries following exposure. *A*, brain of a cat into which 20 cc. of a solution of trypan red was injected immediately after the exposure and the animal killed twenty-four hours later. *B*, brain of a control animal, in which the same solution was injected, but no exposure was performed. Only the dura is stained.

repeated the following day and the animal killed a few hours later. Postmortem examination of the brain (fig. 9) showed that the whole cerebrum was slightly but definitely stained by the dye. The exposed area, however, was much more darkly stained, so that it was clearly outlined from the rest of the cortex. The gray matter was more stained than the white, owing to the greater number of vessels. The choroid plexuses, the tuber cinereum and pituitary and the area postrema were all darkly stained. The anterior part of the brain (cortex) was paler than the posterior, and, as a rule, the base was paler than the convexity. In coronal sections of the brain one could see that the staining was not quite uniform but that patches of darker color spread out, without following any characteristic distribution. The subcortical structures —the striatum, the thalamus and the hypothalamus—might in some cases be rather deeply stained, especially those in which the swelling of the brain was obvious. The blue color of the brain disappeared almost completely in the sections cut for histologic examination, even if they were very thick. Interestingly, not much of the dye could be seen inside the vessels (and most of them did not have any at all). This is important, since Spatz,[3] in his experiments with massive intravital injections of trypan blue in rabbits, described a light blue tinge of the brain which he concluded was due to the presence of the dye inside the capillaries. However, in the illustrations he showed the capillaries in blue, whereas the cerebral substance was quite unstained. Examination under an immersion oil lens of thin, unstained sections of the brains of our animals showed many minute granules of the dye scattered throughout the brain, around the vessels, in the perivascular spaces and even inside the cells. The scanty amount of blue which remained inside the vessels and the presence of these granules in the brain tissue are evidence of the passing of the dye across the capillary endothelium.

Von Möllendorff's studies[4] with intravital injections of trypan blue demonstrated first that ectodermal elements of the brain—neurons and both types of neuroglial astrocytes and oligodendroglial cells—do not have any affinity for the dye except in conditions of damage. He found minute granules of trypan blue in the cytoplasm of only the damaged neurons and neuroglial cells; dead cells were diffusely stained; well preserved, undamaged cells, however, remained completely unstained. Later, King[5] demonstrated again the lack of affinity of the ectodermal cells for the trypan blue on this basis, and he questioned the existence of the blood-brain barrier.

Our studies showed that to a certain extent neurons can retain small amounts of trypan granules if they are damaged or swollen, but we failed to see any dye at all in the apparently

3. Spatz, H.: Die Bedeutung der vitalen Färbung für die Lehre von Stoffaustausch zwischen dem Zentralnervensystem und übrigen Körper, Arch. f. Psychiat. **101**:267, 1934.

4. von Möllendorff: Vitale Färbung an tierischen Zellengrundlage: Ergebnisse und Ziele biologischer Farbstoffversuche, Ergebn. d. Physiol. **8**:141, 1920.

5. King, L. S.: The Hematoencephalic Barrier, Arch. Neurol. & Psychiat. **41**:51 (Jan.) 1939.

normal cells. In slides stained with silver carbonate methods, we could follow the behavior of the microglial cells. It is out of the realm of this paper to discuss cytologic problems concerning this interesting question. Suffice it to say that microglial cells become activated as a result of the exposure because they have to phagocytose red blood cells, and probably products from disintegrated neurons. But when, in addition, the trypan blue is injected, the degree

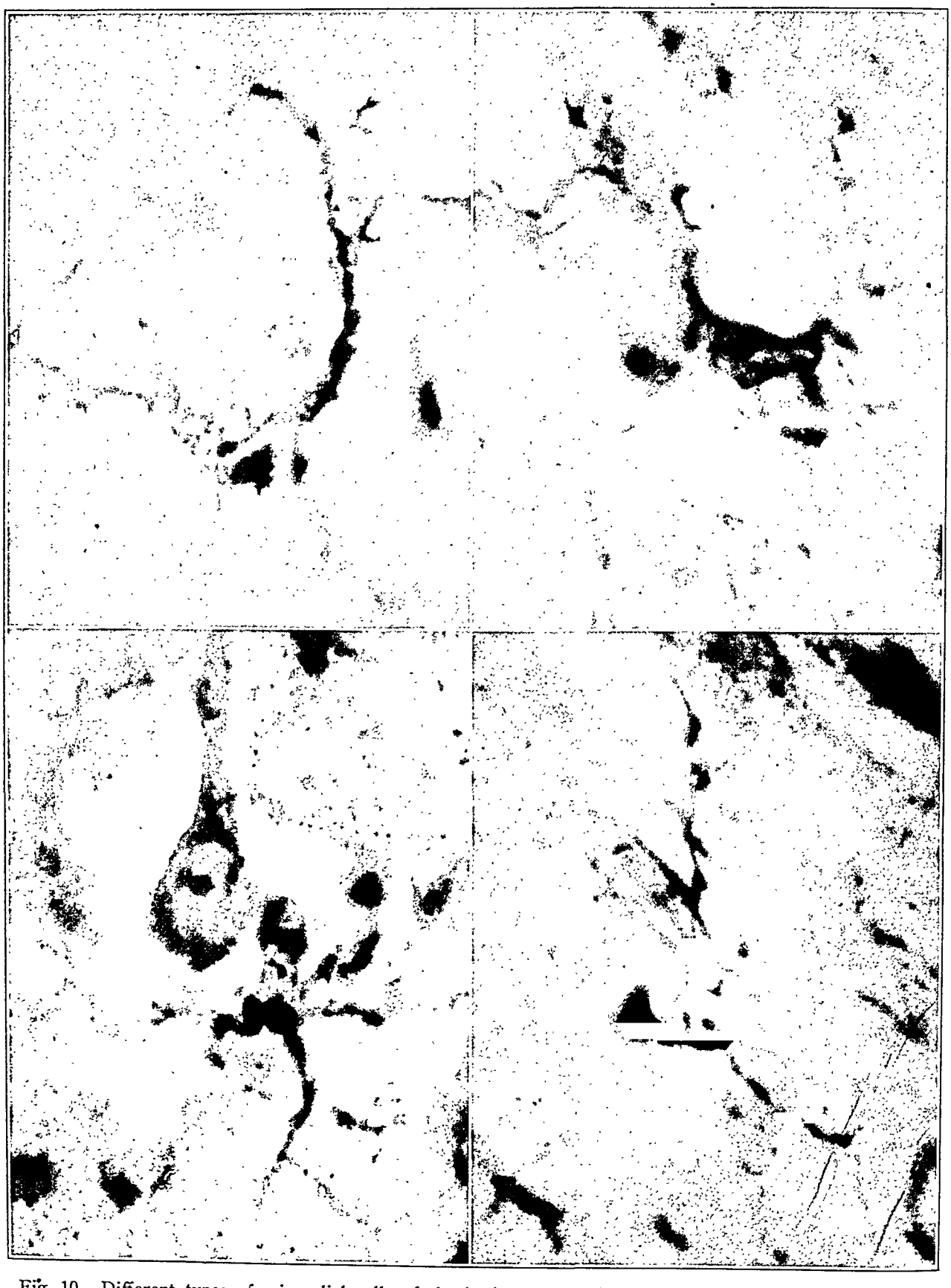


Fig. 10.—Different types of microglial cells of the brain of a cat following exposure and injection of trypan blue, showing phagocytic activity. Silver carbonate stain.

of activity is more manifested (fig. 10). Large, dark granules are seen inside the body of the microglial processes. No doubt some of these granules represent debris of the blood cells and other products of disintegration resulting from the circulatory alterations, but most of them are stored-up precipitate of the trypan dye. Since our first experiments, we have been impressed by the fact that many more and thicker granules were seen in the slides stained with the silver carbonate methods than in either the unstained sections or the sections stained simply with carmine. Further in vitro experiments convinced us later that the silver carbonate solution precipitates the colloidal trypan solution in coarse, dark granules; this explains the difference between the picture observed in the unstained sections and that in sections stained with the metallic methods. In the latter we always could see a larger number of coarse granules, both in the intercellular spaces and in the cells, than in the former. This was also particularly evident inside and around the vessels, where granules could be seen with the silver technic which were absent in the carmine-stained or in the unstained sections. Apparently, the lack of affinity of the ectodermal elements for the trypan dye resulted in most of the solution being maintained in a colloidal state until the later presence of the silver carbonate altered it and helped the formation of the coarse precipitate.

## COMMENT

Spielmeyer [6] first investigated the pathologic changes in the brains of patients dying of various forms of vascular disease which were supposed to produce cerebral anemia. He described various types of neuronal alterations in the cortex which he considered characteristic of cerebral ischemia. The cellular changes were characterized by swelling, shrinkage, liquefaction or coagulation of the neuron, each one of them giving a more or less typical histologic picture. A few years later, Gildea and Cobb [7] produced cerebral anemia experimentally in cats and studied the brains microscopically. All cats in which symptoms of pronounced cerebral anemia developed showed lesions in the cerebral cortex. The neurons were characteristically shrunken and darkly stained with irregular nuclei. Swollen cells and chromatolysis were also found when the anemia was sufficiently complete. Areas of devastation, showing absence of many cells and interrupting the normal orderly lamination, were frequently observed. Although these focal areas of necrosis required at least twenty-four hours to appear, shrinkage, chromatolysis and homogeneous staining of the cells appeared immediately after prolonged anemia. This work confirmed the postmortem studies by Spielmeyer on the human brain and supported his view that the morphologic changes were due to ischemia.

In our studies, the types of cellular alteration corresponded with the description by these investigators. We observed, as did Gildea and Cobb, that shrinkage and homogeneous staining of the cells were much more conspicuous and more frequent than chromatolysis, swelling and liquefaction and that no correlation existed between the clinical condition of the animals and the pathologic changes in the cells. In our opinion, the ischemia observed after the dilatation which followed the exposure is sufficient to account for these cellular changes. The increase of permeability of the capillary endothelium demonstrated by the diapedetic hemorrhages and the trypan blue experiments explains the increase in the bulk of brain tissue as a result of the abnormal accumulation of fluid in the cerebral parenchyma. Certainly, the degree of increase in volume of the brain varies a great deal from one experiment to another. On the other hand, the histologic picture of the cellular and vascular changes, with the conspicuous widening of the Obersteiner and the Virchow-Robin spaces, presents a more constant feature. Circulatory changes are, therefore, the most important factor from a pathogenic point of view in the reaction of the brain after exposure.

The pathologic picture of edema of the brain is described as rarefaction and hydration of the tissue spaces, which give the brain an areolar, honeycombed appearance, dilatation of the periganglionic and perivascular spaces and increase in the protoplasmic astrocytes, which may show also a tendency to ameboid degeneration. Recent investigators have stressed the importance of circulatory changes in the pathogenesis of edema. Scheinker [8] stated that the histologic picture of cerebral swelling includes morphologic signs of vascular alterations, with an increase in the permeability of the vessel walls, widening of the perivascular and perineuronal spaces by outflow of fluid from the vessels. areolar appearance of the tissue, vascular stasis

6. Spielmeyer, W.: Histopathologie des Nervensystems, Berlin, Julius Springer, 1922.

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

8. Scheinker, I.: Cerebral Swelling and Edema Associated with Cerebral Tumor: Histogenetic and Histopathologic Study, Arch. Neurol. & Psychiat. **45**: 117 (Jan.) 1941.

and diapedesis. He concluded that vascular alterations are the fundamental features in the genesis of the swelling and that the difference between edema and swelling is only a matter of degree, the edema showing morphologic changes in the vessels which are not found with swelling.

Greenfield [9] also did not accept the view (held by Spatz and others) that edema and swelling are different processes. With the edema accompanying brain tumors he described degeneration of the myelin and swelling and varicosities in the myelinated axons, swelling of astrocytes and moderate activation of the microglia. He expressed the belief that the presence of an excess of interstitial fluid interferes with the adequate diffusion of oxygen from the vessels to the cells.

Nieto and Caso (cited by Obrador Alcade [10]) in experimental acute swelling of the dog brain failed to find any morphologic changes in the neurons or in the interstitial cells, myelin and axons also being apparently normal. Only the widening of the perivascular spaces was evident.

Our experiments show that the vessels of the brain undergo an increase in permeability and certain morphologic changes which would lead us to agree with Scheinker's point of view that the circulatory changes are essential to explain the excess of fluid in the tissue spaces which is the fundamental feature in any edematous condition.

Finally, our experiments demonstrate also that in a strict sense the increase in the brain bulk cannot be accepted as *conditio sine qua non* for the diagnosis of cerebral edema. Only when the amount of interstitial fluid is exaggerated will the volume of the brain be increased. In milder reactions, such as those in most of our exposure experiments, one sees only the histologic picture of edema without much change in the volume of the brain.

## SUMMARY AND CONCLUSIONS

When an area of cerebral cortex in one hemisphere of the cat brain is exposed to the air for several hours, an acute reaction of brain tissue takes place which persists up to the fourth or fifth day after closure of the exposure wound.

This reaction is more severe in the exposed area but is also evident in more remote regions of both hemispheres and in the subcortical structures. It is characterized by both circulatory and cellular changes.

Grossly, the circulatory changes appear first as a brief period of venous dilatation and engorgement, followed by active congestion due to arterial dilatation, which reaches its maximum about two hours after the beginning of the exposure, at which time the pulsating movements of the brain with respiration disappear and some cerebral swelling may be noticeable. The degree of this swelling varies greatly from one experiment to another: In some cases an actual herniation of the exposed area is present, whereas in others the increase in volume is scarcely perceptible.

Microscopic examination of sections shows scattered diapedetic hemorrhages throughout both hemispheres in the gray and white matter and in the subcortical structures. They are, however, more conspicuous in the exposed area. If the degree of cerebral swelling is very pronounced, actual hemorrhages, with loss of continuity of vessel walls, are seen. Twenty-four hours after the exposure, areas of ischemia are present throughout the whole cortex, particularly in the exposed area; veins are still dilated and engorged, but some arteries are empty. The capillaries are collapsed and empty, or they may show engorgement with blood cells. The perivascular spaces are extremely distended, and the permeability of the capillary endothelium is increased. Three days after the exposure, the circulation is practically reestablished; a few vessels may still show aneurysm-like dilatations where their damaged walls have not yet recovered.

The cellular changes appear early and are characterized by swelling and chromatolysis or shrinkage and homogenization. Some neurons undergo complete destruction, and occasional zones of devastation can be seen. As with the circulatory changes, the neuronal alterations also clear up by the third day after exposure, and, except for the permanent destruction of a few neurons, the histologic picture at that time may be completely normal. Microglial cells show a mild reaction of brief duration, which is, however, more evident when trypan dyes have been injected. The neuroglia gives only slight response to the exposure. This is manifested by moderate hyperplasia, followed by gliosis confined mostly to the exposed area, especially in the pial neuroglia, which may be the only region where any visible neuroglial change remains. The oligodendroglia shows no change whatever.

1025 Pine Avenue West.

9. Greenfield, J. G.: The Histology of Cerebral Edema Associated with Intracranial Tumors (with Special Reference to Changes in the Nerve Fibers of the Centrum Ovale), Brain **62**:129, 1939.

10. Obrador Alcalde, S.: Cerebral Edema, An. méd. **3**:31, 1942.

# TREMORS OF COMBAT NEUROSES

## COMPARISON WITH TREMORS OF PARALYSIS AGITANS, DELIRIUM TREMENS AND THE PSYCHONEUROSES OF CIVILIAN LIFE; ELECTROMYOGRAPHIC STUDIES

MARY A. B. BRAZIER, PH.D.

BOSTON

The acute neuroses of war are in many ways unlike any syndromes seen in peacetime civilian life. In World War II the first severe neuroses were seen in the men evacuated from the beaches at Dunkerque. These men showed several outstanding symptoms, many of which have since been described in the literature. They had all been exposed to severe strain; all were exhausted and dehydrated and in most cases had had no sleep for four days. In addition to the trial of physical endurance, they had been in continuous danger of death and had been exposed to the repeated trauma of seeing men die violent deaths.

One frequent symptom was a gross tremor, usually of the hands, and in many cases this tremor was so marked that the diagnosis of paralysis agitans was in question. This diagnosis was supported by the facies, which was often masklike in its listlessness and apathy. In the course of another line of investigation, which included observations on the arm, one characteristic of these tremors was very striking, and this is the subject of the present paper. In these patients the tremor often appeared to be a rhythmic jerking of the whole limb without the alternation of flexion and extension seen in tremors of paralysis agitans. Unfortunately, no electromyograph was available at that time in the hospital in which these patients were being studied (Sutton Emergency Hospital, England).

In the electromyographic laboratory at the Massachusetts General Hospital it has now been possible to make electromyographic studies of similar tremors in cases of combat neuroses. All the subjects studied were patients from the United States Naval Hospital at Chelsea, Mass., and the investigation was undertaken under a project from the Bureau of Medicine and Surgery of the United States Navy (Project No. X369 Gen. 54).[1]

Although a longer period had elapsed between the combat experience and the examination of these men than occurred in the case of the Dunkerque survivors, tremor was still an outstanding symptom.

The purpose of this study was an attempt to use the electromyograph in making a differential diagnosis of tremors due to lesions of the extrapyramidal system, tremors of psychogenic origin and tremors due to metabolic disorders or drug intoxications. The tremors of basal ganglia origin are usually classified in three groups: tremors due to degeneration in the basal ganglia consequent to arteriosclerosis in senile persons; tremors due to lesions which are the sequelae of encephalitis, and post-traumatic tremors presumably associated with some lesion in the basal ganglia, such as damage to small blood vessels. Because of the age range of these service men, the last two types only need be considered.

### METHOD

For the recording of electromyograms, a three channel ink-writing oscillograph, such as is standard for electroencephalographic technic, was generally used, although in some cases in which simultaneous multiple recordings from many muscles were required, a six channel machine was employed. Since in this study the interest lay in the behavior of the muscle as a whole rather than in the single motor unit, the electrode technic used consisted of the employment of small, flat solder disks, approximately 1 cm. in diameter, pasted on the skin over the belly of the muscle under observation. The currents from the muscles were amplified in the usual manner, the electromyographic technic being in general similar to that described in other studies of muscle potentials.[2]

From the Department of Psychiatry, Massachusetts General Hospital.

This study was aided by a grant from the George Harrington Trust Fund.

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth are those of the writer and are not to be construed as reflecting the policies of the Navy Department.

1. Lieut. Comdr. Herbert I. Harris (MC), U.S.N.R., furnished the clinical histories of the Navy personnel used in this study. Dr. Harris left for duty overseas before the electromyographic data were worked up, and he is therefore not responsible for any opinions stated in this paper.

2. Schwab, R. S.; Watkins, A. L., and Brazier, M. A. B.: Quantitation of Muscular Function in Cases of Poliomyelitis and Other Motor Nerve Lesions, Arch. Neurol. & Psychiat. **50**:538-545 (Nov.) 1943.

Previous work in this laboratory, in collaboration with Comdr. Robert S. Schwab (MC), U.S.N.R., and in other laboratories has established certain characteristics of the tremor of paralysis agitans. This tremor is usually in the frequency range of 4 to 7 cycles per second and is of great regularity in any one patient; Schwab and Cobb [3] have shown the maximum variation in any one muscle group to be 10 per cent, but it is commonly much less than this. The form of the electrical potentials is also characteristic, being a smooth build-up to a maximum spike followed by a smooth decrease to relaxation, with a period of comparative quiet between the individual tremor bursts. An example of the tremor of paralysis agitans is shown in figure 1.

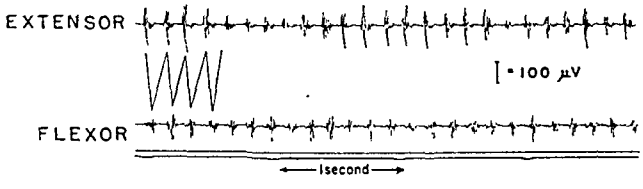



Fig. 1.—Tremor in a case of paralysis agitans (case 4, table 2). Note the regularity of pattern and frequency and alternation of the tremor bursts from extensor to flexor muscle.

Another characteristic of the tremor of paralysis agitans demonstrable by the electromyogram is that when simultaneous recordings are made from opposing muscles at rest, as, for example, from the extensors and flexors of the forearm, the tremor potentials are out of phase in the antagonistic muscles (fig. 2). The alternation


Fig. 2.—Tremor in a case of paralysis agitans. The tracing has been enlarged to demonstrate the alternation of action potentials from agonist to antagonist muscle.

of flexion and extension is well known and produces the typical pill-rolling movement of paralysis agitans. It is not to be confused with the opposite phenomenon of disordered reciprocal innervation present in rigid muscles on voluntary movement. This has been described by Hoefer and Putnam.[4]

3. Schwab, R. S., and Cobb, S.: Simultaneous Electromyograms and Electroencephalograms in Paralysis Agitans, J. Neurophysiol. **2**:36-41, 1939.

4. Hoefer, P. F. A., and Putnam, T. J.: Action Potentials of Muscles in Rigidity and Tremor, Arch. Neurol. & Psychiat. **43**:704-725 (April) 1940.

These three characteristics of the electromyogram of the tremor of paralysis agitans formed the nucleus for observation on the tremor of combat neurosis—that is, the frequency, the electromyographic pattern and the alternation in opposing muscles at rest.

## RESULTS

In this series, 23 cases of tremor among service personnel were investigated. In 3 of these 23 cases the neurologic examinations gave evidence of tremor of postencephalitic paralysis agitans, and they are omitted from the classification of combat neurosis. These 3 cases will be presented in detail later, but in brief summary it may be said that in each of these cases the tremor had a frequency of 6 to 7 cycles per second and showed extreme regularity. The bursts in the extensors and the flexors were out of phase, and at no time did they occur synchronously.

In the other cases in which the diagnosis was combat neurosis, no tremor slower than 8 cycles per second was found. Synchrony between opposing muscles was common, and in some cases spontaneous diphasic spikes were found in the

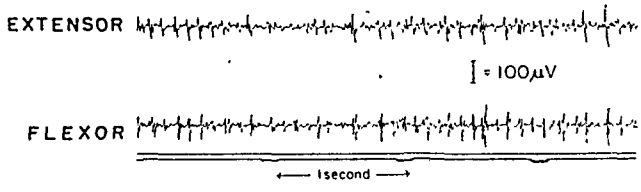



Fig. 3.—Tremor in a case of combat neurosis (case 13, table 1). Note the fast frequency, the irregularity of the bursts and the frequent synchrony between opposing muscles.

resting muscles. The cases have been briefly summarized in table 1, and a typical electromyogram of a tremor of psychogenic origin (case 13) is shown in figure 3.

Study of table 1 gives several items of information about the tremors in these cases. It will be noticed that whereas all the cases in the table are classified under the diagnosis in current Naval usage, i. e., combat neurosis, there is made in the fourth column some slight breakdown of this overall diagnosis from the patient's symptoms and history.

A brief description of the type of tremor is given in the fifth column, and in the sixth column is a note as to alternations of the tremor from agonist to antagonist groups.

When one looks for the characteristics which have been listed as typical of the electromyograms of the tremor of paralysis agitans, they are conspicuously absent in this series, with the single exception of case 14. In the first place,

the frequency of the tremor is often so fast as to give a completely diffuse electromyogram, with no discernible rhythm; the clearcut pattern of the rhythmic muscle discharge seen in the tremor of paralysis agitans is entirely absent (compare, for example, figures 2 and 3 with figure 1). There are also no clear interspaces between the tremor bursts (again, with the exception of case 14). Finally, there is no alternation of the tremor from flexor to extensor groups, with, once more, the exception of case 14.

hospital he was discharged as well, but one month prior to the test he first noticed disturbance of gait and onset of tremor. He also had insomnia, anorexia, nausea, vomiting, diarrhea and frequent headaches. His attitude toward his symptoms was expressed as follows: "All I need to get well is to have no one paying attention to me all the time. If these doctors would lay off. If people wouldn't try to help me. I try to walk straight."

His childhood history revealed finickiness toward food, rare nightmares and night talking but no sleepwalking. He had no history of enuresis, nail biting or spells of any kind.

On neurologic examination there were a pronounced tremor of the arms and considerable disturbance of gait.

TABLE 1.—*Electromyographic Data on Tremor in Cases of Combat Neurosis*

| Case No. | Patient | Age | Diagnosis | Type of Tremor | Presence or Absence of Synchrony in Antagonists |
|---|---|---|---|---|---|
| 1 | M. K. | 29 | Anxiety neurosis with chronic tremor since age of 12 | On extension only; 8-10 per sec. | No tremor in flexors |
| 2 | W. P. | 26 | Acute anxiety state | Very gross, diffuse and irregular; no clear interspaces | Diffuse tremor in antagonists |
| 3 | M. Q. | 35 | Anxiety neurosis; many early psychoneurotic traits | Diffuse with no definite frequency; no clear interspaces | Diffuse tremor in antagonists |
| 4 | C. Y. | 30 | Psychoneurosis neurasthenia | Mostly diffuse, never slower than 10 per sec.; no clear interspaces | Often synchronous |
| 5 | J. S. | 33 | Anxiety neurosis in a constitutional psychopath | Diffuse tremor in extensors; no clear interspaces | Diffuse tremor in antagonists |
| 6 | B. P. | 29 | Hysteria | 8-9 per sec.; no clear interspaces | Asynchronous |
| 7 | E. M. | 22 | Anxiety neurosis | Gross spasms of no definite frequency | Often synchronous |
| 8 | H. J. | 32 | Anxiety neurosis | Gross twitches of no definite frequency | Often synchronous |
| 9 | W. M. | 22 | Operational fatigue | Diffuse with no definite frequency; no clear interspaces | Synchronous |
| 10 | S. W. | 40 | Mixed psychoneurosis | Diffuse tremor on extension only; at least 10 per sec., with no clear interspaces | No tremor in flexors |
| 11 | D. M. | 21 | Anxiety and depression | Irregular, 8-9 per sec.; no clear interspaces | No tremor in antagonists |
| 12 | W. H. | 35 | Depression with anxiety | Irregular, 8-10 per sec.; no clear interspaces | No tremor in antagonists |
| 13 | G. H. | 24 | Anxiety neurosis | Irregular, but approximately 10 per sec. | Often synchronous |
| 14 | R. C. | 21 | Post-traumatic anxiety neurosis with hysteria | 8 per sec., with clear interspaces | Alternating from flexors to extensors |
| 15 | H. H. | 37 | Anxiety neurosis | Diffuse tremor on extension, not less than 9 per sec.; no clear interspaces | Sometimes synchronous |
| 16 | A. B. | 19 | Operational fatigue | Very fast, diffuse tremor; no definite frequency; no clear interspaces | Diffuse tremor in antagonists |
| 17 | R. R. | 22 | Anxiety neurosis | Very slow, 3 per sec., tremor on extension; no clear interspaces | Not present in flexors |
| 18 | R. M. | 24 | Anxiety neurosis | 7-8 per sec. but very irregular; interspaces not very clear | Synchronous in antagonists |
| 19 | J. J. | 42 | Anxiety neurosis | Diffuse tremor with no clear interspaces; frequency approximately 10/12 per sec. | Present in extensors and flexors and sometimes exactly synchronous |
| 20 | W. A. | 24 | Anxiety neurosis | Diffuse tremor on volitional movement only; irregular with no clear interspaces; frequency varies from 7-11 per sec. | Present in opposing muscles but not exactly synchronous |

Not only do these tremors fail to alternate from agonist to antagonist, but in some cases the discharges are truly synchronous in the opposing muscles; i. e., the individual spikes of muscle discharge occur exactly synchronously in antagonists (fig. 4, case 18).

Since in case 14 the electromyogram proved to have such consistently exceptional features, the symptoms and history will be given in rather more detail.

CASE 14.—R. C., a 21 year old seaman, forward gun captain, had served on three ships (transports and tankers). Eight months previous to the test he fell through an open hatch 35 feet (10.6 meters) to the deck below. He stated that "his back was broken" and that he lost consciousness. After several months in the

This was not the forward-leaning, propulsive type of gait common in patients with paralysis agitans but, rather, a lurching gait with buckling of the left knee. No rigidity or excessive salivation was noted.

This one exception to the pattern of the electromyogram in this series of cases of combat neurosis is found also to be the only case of tremor of post-traumatic origin. The obvious question arises as to whether this case may not be one of tremor of early paralysis agitans consequent to injury, and the patient's attitude toward his symptoms may contribute to this opinion.

The 3 cases among these service men in which the diagnosis was tremor of postencephalitic

paralysis agitans can be summarized briefly as follows:

L. C., a 31 year old seaman, presented the following symptoms: cogwheel rigidity of the arms and legs; tremor of the hands, arms and legs; spastic gait; dizzy spells with blurring of vision, and tremor, most marked in the legs, where it alternated from the anterior tibial to the gastrocnemius muscle. He had a history of diphtheria with delirium at the age of 8 years. The electromyogram showed a very regular tremor, of 6 per second frequency, of smooth pattern and with clear interspaces. The diagnosis was postencephalitic paralysis agitans.

P. G., a 34 year old seaman, had tremors of the hand, tongue, head and right leg, dating from an attack of influenza in 1918. The right side of his face was

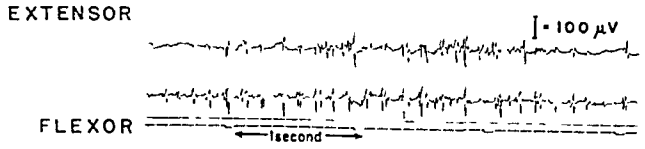



Fig. 4.—Tremor in a case of combat neurosis (case 18, table 1). Note the irregularity of the tremor and the synchrony of many of the discharges.

smoothed out. There was a pill-rolling movement of the thumb and finger of the right hand. There was no loss of associated movements or excessive salivation. The electromyogram showed a regular, 7 per second tremor of smooth pattern, alternating from flexor to extensor, with almost clear interspaces between the tremor bursts. The diagnosis was postencephalitic paralysis agitans.

K. M., a 36 year old seaman, had tremor of the right arm, diminution of associated movements in the right arm on walking and a slight stoop suggestive of rigidity of the neck characteristic of paralysis agitans. He had a history of pneumonia with delirium at 9 years of age, blood poisoning with delirium at 22, head injury with loss of consciousness at 33 and a second head injury with loss of consciousness at 35. The electromyogram showed a 6 per second tremor, alternating from flexor to extensor. The diagnosis was early paralysis agitans following multiple cerebral trauma (fig. 5).

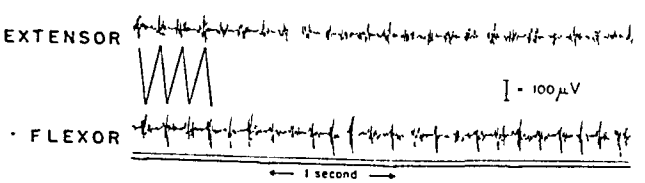



Fig. 5.—Tremor in a case of paralysis agitans (K. M., a 36 year old seaman). Note the regularity of rhythm, the 6 per second frequency and the alternation of tremor bursts from flexor to extensor muscle.

In this small series of cases occurring among service personnel, all of whom had seen combat, some differentiating characteristics have appeared in the electromyograms in 20 cases of combat neurosis as compared with the electromyograms in 3 cases of paralysis agitans. These differentiating features were in the main as follows:

1. The frequency of tremors seen in the combat neuroses is in general much faster and more diffuse than that of the tremor of paralysis agitans, and in cases in which the rhythm is well defined it is usually irregular in timing.

2. There is rarely a clear space between the tremor bursts, the potentials usually being diffuse, with some waxing and waning of the voltage, which coincides with the tremor movement.

3. The burst of potential accompanying the tremor movement does not have a smooth build-up to the maximum voltage followed by a smooth decline, such as is usually found in the tremor of paralysis agitans, but has a much more irregular pattern, of great variability.

4. In the cases of combat neurosis the tremor does not alternate from agonist to antagonist and is often even exactly synchronous in opposing muscles.

Since this series is small, it may be of interest to compare these records with the electromyograms in some civilian cases of paralysis agitans and of tremor of other origins.

In table 2 are summarized the observations in 10 cases of paralysis agitans from the wards and the outpatient department of the Massachusetts General Hospital.

It will be seen that an outstanding characteristic in all these cases is the regularity of the tremor. In every case the rhythm was well marked and of a frequency slower than is found in the cases of combat neurosis. In all these 10 cases the frequency was in the range of 4 to 7 cycles per second. In each of the 6 cases in which electromyographic data were obtained for antagonist muscles the tremor was found to alternate in opposing muscles. One of these (case 4) is illustrated in figure 1.

There are also data on 10 cases of civilian psychoneuroses, and these have been summarized in table 3. These cases were all from the psychiatric wards and the outpatient department of the Massachusetts General Hospital. In these cases the tremors were in general much less gross than in the cases of combat neurosis, with the single exception of case 6, which is illustrated in figure 6.

Here, as in the cases of combat neurosis, the tremors were fast in frequency, diffuse in pattern and irregular in timing. Irregularity of rhythm in hysterical tremors was described and demonstrated electromyographically by Cobb, in 1920.[5]

5. Cobb, S.: Electromyographic Studies of Muscles During Hysterical Contraction, Arch. Neurol. & Psychiat. **4**:8-15 (July) 1920.

In no case in the present series did the tremor alternate from agonist to antagonist. In some cases the exact synchrony of discharges in opposing muscles was striking, as, for example, in case 6 of table 3. This is the case illustrated in figure 6.

Another type of tremor on which some electromyographic data are available is the alcoholic tremor. An example of such a tremor in the case of a patient admitted in delirium tremens is shown in figure 7. In this case the tremor is rather slower than most tremors of paralysis agitans (4 per second) and is fairly regular in pattern but is markedly synchronous in extensor and flexor groups.

There is another differentiating characteristic of these tremors which has not been dealt with here, since it is easily detectable with the naked eye and one does not need the help of an electromyogram to determine it. This is the observation that the tremor of paralysis agitans is usually more intense in the resting state and tends to decrease with the patient's attempt at a fine movement, whereas the reverse is true with the tremor of psychoneurosis; the latter usually becomes far more severe with intention.

TABLE 2.—*Electromyographic Data on Tremors of Paralysis Agitans*

| Case No. | Patient | Age | Diagnosis | Type of Tremor | Alternation in Antagonists |
|---|---|---|---|---|---|
| 1 | H. R. | 48 | Postencephalitic paralysis agitans | Regular, 5 per sec. tremor of right arm with clear interspaces | Alternation from extensor to flexor |
| 2 | H. B. | 25 | Post-traumatic paralysis agitans | Regular, 5 per sec. tremor of left arm; clear interspaces | Alternation from extensor to flexor |
| 3 | M. F. | 23 | Postanoxic paralysis agitans | Regular, 5-6 per sec. | No data |
| 4 | A. P. | 61 | Arteriosclerotic paralysis agitans | Regular, 6 per sec. | Alternation from gastrocnemius to anterior tibial muscle |
| 5 | E. B. | 35 | Postencephalitic paralysis agitans | Very regular, 5 per sec. | No data |
| 6 | J. C. | 35 | Post-traumatic paralysis agitans | Regular, 5 per sec.; clear interspaces | Alternation from flexor to extensor |
| 7 | F. E. | 68 | Arteriosclerotic paralysis agitans | Regular, 5 per sec. | No data |
| 8 | A. T. | 54 | Right-sided paralysis agitans | Regular, 4 per sec.; clear interspaces | No data |
| 9 | F. S. | 28 | Congenital dysfunction of extrapyramidal system | 7 per sec., irregular in pattern | Alternation in antagonists |
| 10 | J. J. | 71 | Paralysis agitans | Regular, 4 per sec. tremor | Alternation in antagonists |

TABLE 3.—*Electromyographic Data on Tremors in Civilian Cases of Psychoneuroses*

| Case No. | Patient | Age | Diagnosis | Type of Tremor | Alternation in Antagonists |
|---|---|---|---|---|---|
| 1 | C. S. | 31 | Mixed psychoneurosis with hypochondriasis | Diffuse, irregular tremor in arm; some rhythm at 11-13 per sec. | None |
| 2 | M. G. | 33 | Anxiety neurosis with depression | Diffuse; some rhythm at 11 per sec. | None |
| 3 | K. G. | 38 | Hysteria with anxiety | Irregular, with variable frequency; never less than 12 per sec. | Often synchronous in extensor and flexor |
| 4 | M. S. | 27 | Conversion hysteria | Very diffuse; some rhythm at 7 per sec. | Some synchrony between extensor and flexor |
| 5 | V. M. | 18 | Hysteria | 5-6 per sec.; irregular pattern | Synchronous in extensor and flexor |
| 6 | C. B. | 21 | Hysteria with psychopathic behavior | Extremely irregular, rhythm varying from 3-15 per sec. | Always exactly synchronous in opposing muscles |
| 7 | O. R. | 26 | Mixed psychoneurosis with hysteria and hypochondriasis | Very diffuse, with no defined pattern | Continuous in opposing muscles |
| 8 | G. G. | 26 | Anxiety neurosis | Bursts of potentials of approximately 2 per sec. | Synchronous in flexor and extensor |
| 9 | E. D. | 21 | Hysteria | Diffuse, with no definite rhythm | Continuous in opposing muscles with some synchronous spikes |
| 10 | D. H | 27 | Hysteria | Diffuse, with some irregular rhythm, from 10-12 per sec. | Often synchronous in opposing muscles |

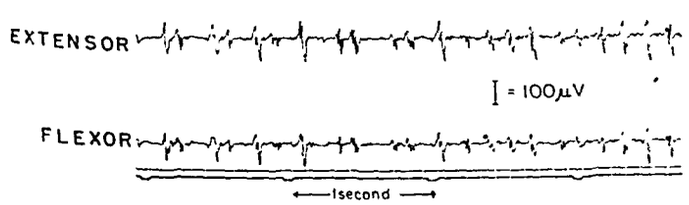



Fig. 6.—Tremor in a case of hysteria (case 6, table 3). Note the irregularity of the bursts and the exact synchrony between the individual discharges in extensor and flexor muscles.

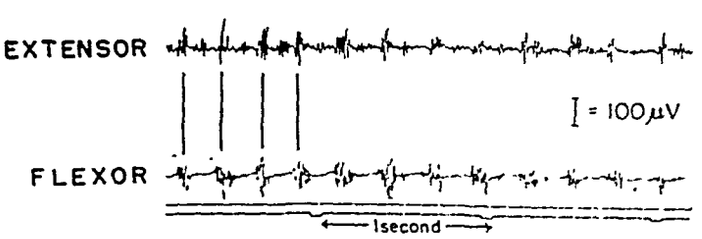



Fig. 7.—Tremor in a case of delirium tremens. Note the slow rhythm and the synchrony of tremor bursts in opposing muscles.

The tremor of paralysis agitans is thought to be due to loss of controlling impulses from the extrapyramidal system which integrate involuntary movement patterns, locomotion and the stabilization of posture.[6] The primitive type of innervation pattern which impairment of these regulating mechanisms releases results in a fairly consistent electromyographic picture in the muscles involved. But the mechanism by which the tremor is caused is still far from clear. There is, for example, the observation of Wechsler [7] that the tremor of paralysis agitans can be abolished by obliterating the arterial pulse by a tourniquet on the limb; there are the various attempts to abolish the tremor by partial section of the motor tracts of the spinal cord (Putnam [8]), by section of the precentral cortex (Bucy and Case [9] and Klemme [10]) and by section of the ansa (Meyers [11]).

Whatever the mechanism of the tremor of paralysis agitans, it is clear that a very different one is concerned with the tremor of psychoneurosis. The electromyographic pattern is quite different and may give leads for further elucidation of the pathways involved. One feature of the electromyogram is the diffuse nature of the potentials in many cases; in this respect they are similar to action potentials of cortical origin. It would be interesting to check this more closely by the use of needle electrodes in the muscle. Another, and perhaps the most outstanding, feature is the absence of alternation in opposing muscles. The alternate innervation of opposing muscles in paralysis agitans has some similarity to clonus, which is a reflex mechanism in the cord. This clonic type of activity is not seen in the tremors of psychoneurosis.

6. Benda, C. E., and Cobb, S.: On the Pathogenesis of Paralysis Agitans, Medicine **21**:95-142, 1942. Fulton, J. F.: Physiology of the Nervous System, New York, Oxford University Press, 1943. Tower, S. S.: Extrapyramidal Action from the Cat's Cerebral Cortex: Motor and Inhibitory, Brain **59**:408-444, 1936.

7. Wechsler, I. S., in discussion on Pollock, L. J., and Davis, L.: Muscle Tone in Parkinsonian States, Arch. Neurol. & Psychiat. **23**:303-319 (Feb.) 1930.

8. Putnam, T. J.: Operative Treatment of Diseases Characterized by Involuntary Movements (Tremor, Athetosis), A. Research Nerv. & Ment. Dis., Proc. (1940) **21**:666-696, 1942.

9. Bucy, P. C., and Case, T. J.: Athetosis: Surgical Treatment of Unilateral Athetosis, Arch. Neurol. & Psychiat. **37**:983-1020 (May) 1937.

10. Klemme, R. H.: Surgical Treatment of Dystonia, A. Research Nerv. & Ment. Dis., Proc. (1940) **21**:596-601, 1942.

11. Meyers, R.: Modification of Alternating Tremors, Rigidity and Festination by Surgery of Basal Ganglia, A. Research Nerv. & Ment. Dis., Proc. (1940) **21**:602-665, 1942.


## SUMMARY

Electromyographic studies were made on the tremors of 23 men of combat personnel. Of these patients, 3 had symptoms of lesions of the extrapyramidal tract, and 20 had a condition diagnosed as combat neurosis.

In addition, studies were made on 10 civilians with paralysis agitans and 10 civilians with tremors associated with psychoneurosis.

Electromyographic data are given on tremor in a case of delirium tremens.

The following electromyographic differences were found between the tremor of paralysis agitans and tremors of psychoneurotic origin:

1. The rate of tremors associated with psychoneurosis is usually faster than that of tremors of paralysis agitans and is often so fast as to give a completely diffuse electromyogram, with no discernible rhythm.

2. The tremor of psychoneurosis does not have the clearly patterned discharge of smooth increase in the voltage to a maximum followed by a smooth decrease that is typical of tremor of paralysis agitans.

3. Clear interspaces between the individual tremor bursts are rarely found in cases of psychoneurosis.

4. Tremor bursts associated with psychoneurosis do not alternate from agonist to antagonist as in paralysis agitans but usually appear simultaneously in opposing muscles, and sometimes are even exactly synchronous in the timing of the individual discharge.


Comdr. J. M. Henninger (MC), U.S.N.R., continued to make available the facilities for this work after Lieut. Comdr. H. I. Harris had gone overseas, and Miss Margaret Gray gave technical assistance in recording the tremors.

Massachusetts General Hospital.

# ARTERIOVENOUS ANEURYSM OF GREAT CEREBRAL VEIN AND ARTERIES OF CIRCLE OF WILLIS

## FORMATION BY JUNCTION OF THE GREAT CEREBRAL VEIN AND THE STRAIGHT SINUS AND BY THE CHOROIDAL ARTERIES AND ANOMALOUS BRANCHES OF THE POSTERIOR CEREBRAL ARTERIES

BERNARD J. ALPERS, M.D., AND FRANCIS M. FORSTER, M.D.
PHILADELPHIA

Arteriovenous aneurysm of the great cerebral vein (Galen) and the arteries of the circle of Willis is so rare that it seems desirable to record an instance of the condition. Only 2 other cases heve been recorded in the literature [1] and a third [2] is unquestionably a typical example of the disorder.

### REPORT OF A CASE

*History.*—R. L. V., an 18 year old youth, entered the Jefferson Hospital on May 9, 1944 and died on June 16, 1944. He had had headaches since he was 6 years old and had suffered from them intermittently until his death. They were largely frontal in location, and they occurred at an average frequency of one or two a week. His headaches were at first relieved by acetylsalicylic acid and were not so severe as to interfere with his activities. Two months before entrance into the hospital, however, they became more severe, and they then lasted most of the day. In the last month the headaches were accompanied with dizziness, characterized by the movement of objects in the environment. Beyond this there was nothing significant in the patient's story and nothing of importance in the past history.

*Neurologic Examination.*—The patient was somewhat euphoric, highly distractible and rather flippant. His reactions were slow, and his intelligence appeared subnormal. The pupils were equal and regular and reacted promptly to light, in accommodation and to consensual stimuli. The optic nerves were well defined and had good color, and the retinas appeared healthy. The visual fields were full as determined by perimetric test, and visual acuity was 20/20 in each eye. The blindspots were not enlarged. Ocular movements were good in all directions. The corneal reflexes were active. There was no facial weakness. Tuning fork tests revealed normal hearing. There was no weakness of the palate or tongue. There was good power in all the limbs except in the right hand, in which the grip seemed slightly weaker than that in the left. The heel-knee test was performed accurately but with a coarse tremor; the patient tended to lose his balance in standing on either foot alone, and there was a little difficulty in performing the heel-toe test. There was no dyssynergia of the limbs or trunk. The gait was steady. The biceps, triceps, radial, achilles and patellar reflexes were *active and equal on the two sides. There were no* pathologic reflexes. The abdominal reflexes were active. Sensory examination gave normal results for all modalities.

*Laboratory Studies.*—The mental age was 9 and 8/12 years and the intelligence quotient 64 by the Stanford-Binet test. A similar examination seven years previously revealed an intelligence quotient of 73.

Electroencephalographic studies revealed no evidence of a focal lesion and no indication of abnormal brain waves.

Studies of the blood revealed 4,200,000 red cells, 4,100 white cells and a hemoglobin concentration of 75 per cent. The Wassermann reaction of the blood was negative. The urea was 9.2 mg. and the blood sugar 71 mg., per hundred cubic centimeters.

Fig. 1.—Lateral view of the skull, showing the evidence of increased pressure on the inner table of the skull and the crescentic calcified shadow in the posterior portion of the skull.

Urinalysis on five occasions revealed a specific gravity of 1.012 to 1.020, without casts, blood, albumin or sugar. Urea clearance was 50 per cent.

The basal metabolic rate was +4 per cent on one occasion. The sugar tolerance test gave normal results.

Studies of the spinal fluid revealed a pressure of 185 mm. of water, 2 cells per cubic millimeter, a negative Wassermann reaction and a protein content of 51 mg. per hundred cubic centimeters.

Roentgenograms of the skull revealed a pronounced convolutional indentation of the inner table of the skull, with complete destruction of the dorsum sellae and the posterior clinoid processes and apparent enlargement of

From the Department of Neurology, Jefferson Medical College.

1. Russell, D. S., and Nevin, S.: Aneurysm of the Great Vein of Galen Causing Internal Hydrocephalus, J. Path. & Bact. **51**:375, 1940.

2. Jaeger, R.: Personal communication to the authors.

the sella turcica. In the right parieto-occipital region was a crescentic rim of calcification, above which lay irregularly mottled calcified areas.

*Course.*—Because of the history of persistent headache and the evidence of calcification in the roentgenogram, a diagnosis of brain tumor was made in spite of the normal pressure. The latter failed to correspond to the indications of pressure shown in the roentgenogram. Since there were no indications of a localized lesion except for the calcified shadow in the roentgenogram and the inconclusive evidences of incoordination on neurologic examination, pneumoencephalographic examination was deemed advisable. An encephalographic study was made but was not successful in revealing the location of the lesion.

Ventriculographic examination, performed by Dr. Rudolph Jaeger, revealed greatly dilated ventricles. The calcified mass appeared to project into the posterior horn of the right lateral ventricle.

Fig 2.—Ventriculogram, showing filling of one ventricle only, with a calcified shadow appearing on the mesial aspect of the ventricle.

*Craniotomy* (Dr. Rudolph Jaeger).—The right lateral ventricle was opened. The report of the operation follows: "At the glomus of the choroid plexus a large, tortuous mass of arteries and veins was found. These ran toward the base of the skull and connected with the large vessels, supplying an aneurysm about the size of a hen's egg. It was necessary to cut through the floor of the lateral ventricle in order to expose the mass. It lay tightly against the tentorium with its vascular stem of attachment toward the midline. It was apparently an aneurysm of a branch of the circle of Willis, probably the posterior cerebral artery. A part of its wall was calcified, and it had a strong pulsation."

The patient reacted poorly to the operation and died two days after the craniotomy. Necropsy was performed.

*Gross Description of Brain.*—The cerebral hemispheres revealed nothing of significance except a severe degree of internal hydrocephalus, involving all parts of the lateral ventricles. The third ventricle was enlarged. The aqueduct of Sylvius was not dilated, and the fourth ventricle was normal in size. The shape and configuration of the cerebral hemispheres were not unusual, and the cerebral vessels and the meninges over them were normal.

The brain was sectioned horizontally, since it was apparent from the approach through the operative field that a large aneurysm was present. This lay between the cerebral hemispheres. The brain mantle was cut away serially in horizontal sections in order to disclose the aneurysm clearly. After study of its relationships as it lay exposed, it was dissected away carefully in order to disclose its features at lower levels. Photographs and drawings were made at each level before each step in dissection.

The aneurysm lay between the cerebral hemispheres occupying the pineal recess and resting on the tectum mesencephali. It measured 4 by 2.5 by 2.5 cm. It was dome shaped, its broadest portion lying superiorly, with a narrow waist at the point of its union with the vessels of origin. The walls were firm and dense but measured only 2.5 to 3 mm. in thickness. Dissection revealed that the body of the aneurysm arose from the junction of the great cerebral vein (Galen) with the straight sinus, but it was not possible to determine which of the two vessels contributed most to its formation. The probabilities are that the great cerebral vein was most involved, since it was greatly dilated for 1 inch (2.5 cm.) before the aneurysmal sac was reached. Nothing could be determined concerning the other dural sinuses, since these were not dissected out at the time of removal of the specimen.

The point of greatest interest lay in the connection of the aneurysm with the arteries of the circle of Willis. As the aneurysm lay exposed, rich arterial supplies could be followed into it from both choroidal arteries, which lay in a maze of smaller arteries and veins on the floor of each lateral ventricle. Direct communication could be established between the aneurysm and the choroidal arteries. These, in turn, could be traced to communications with the posterior cerebral artery on each side.

The circle of Willis revealed normal anterior cerebral, anterior communicating, vertebral and basilar arteries. The basilar artery divided normally into the two posterior cerebral arteries, but a branch from each posterior cerebral vessel could be followed coursing around the mesencephalon, sending branches into the aneurysm. On the tectum of the midbrain lay a maze of vessels connected with the posterior cerebral arteries, sending many branches into the wall of the aneurysm. From the left middle cerebral artery came an aberrant branch, which was connected with the basilar artery by aberrant vessels enclosing the oculomotor nerve. There were several aberrant branches from the posterior cerebral arteries.

Microscopic examination of the great cerebral vein revealed a hyperplastic intima and a thickened adventitia. The wall of the aneurysm revealed a thickened and hyperplastic intima and an adventitia of abundant, loose connective tissue. There was no evidence of infiltration in the walls of either the vein or its aneurysm.

## COMMENT

Only 2 previous cases of aneurysm of the great cerebral vein have been recorded (Russell and Nevin [1]). The 2 cases reported by Russell and Nevin concerned infants of 17 months. In their

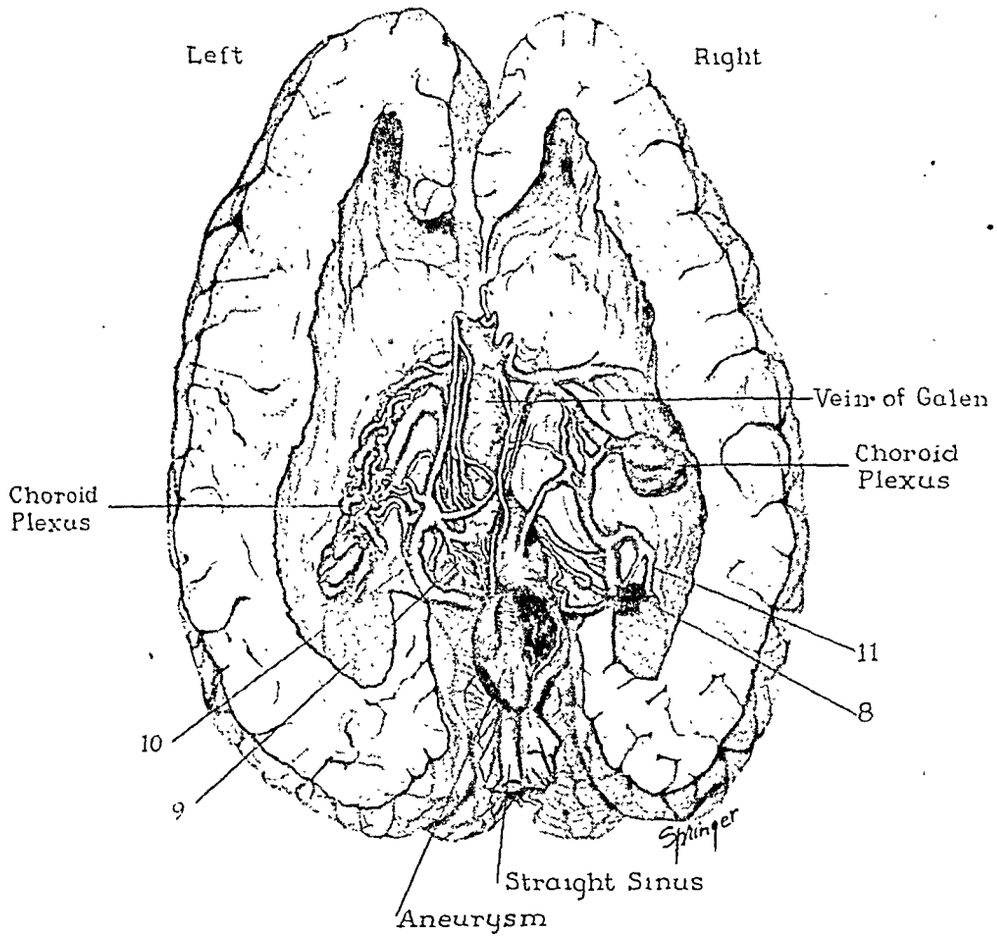



Fig. 3.—Horizontal section of the brain, showing the position of the aneurysm, the great cerebral vein (Galen) and the straight sinus, as well as the arterial supply. In this figure, and in figure 2, the arteries are designated as follows: (*1*) basilar, (*2*) left posterior cerebral, (*3*) left posterior communicating, (*4*) aberrant artery on left, (*5*) right posterior communicating, (*6*) right posterior cerebral, (*7*) aberrant artery on right, (*8*) aberrant artery on right choroidal artery and to aneurysm, (*9*) and (*10*) aberrant artery on left and (*11*) right posterior choroidal.

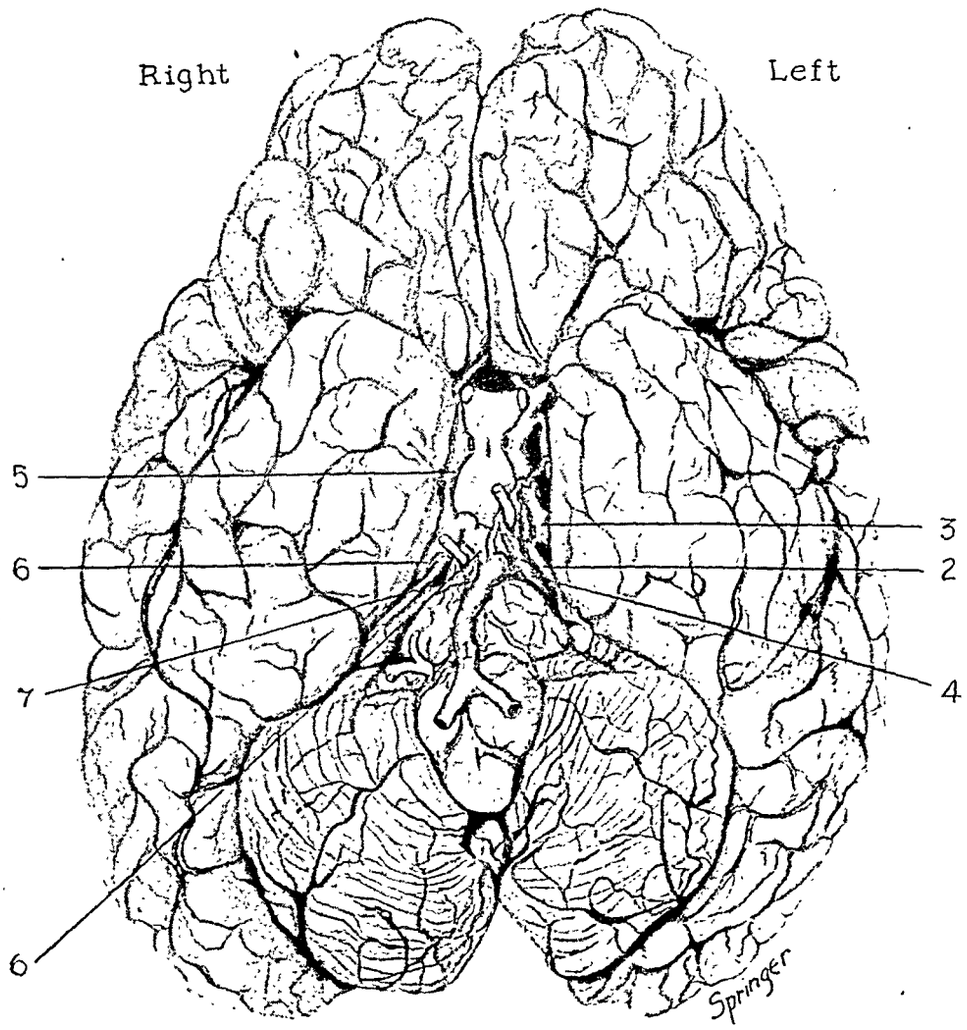



Fig. 4.—View of the base of the brain, demonstrating the anomalies of the circle of Willis and the derivation of the arteries supplying the aneurysm.

first case "the transverse fissure was occupied by a complex arteriovenous aneurysm to which the torcular Herophili, the great vein of Galen and the left posterior cerebral artery contributed." Associated with the aneurysm were anomalies of the venous channels characterized by complete absence of the venous communication with each jugular vein through the jugular foramen. In the second case reported by Russell and Nevin the aneurysm was, similarly, of the great cerebral vein. The case recorded in the present contribution resembles in many respects the cases reported by Russell and Nevin. It occupied the transverse fissure and was composed of a large sac contributed by the great cerebral vein (Galen) and the posterior cerebral arteries.

In the cases previously recorded the venous portion of the aneurysm was contributed by the great cerebral vein and the arterial portion by the posterior cerebral arteries. In the case recorded in the present contribution additional arterial contributions were made by aberrant arteries from the posterior cerebral arteries and by the choroidal arteries, the latter being the direct communication with the aneurysm. The cases recorded thus far have in common not only the derivation of the main aneurysmal wall from the great cerebral vein but a similar arterial origin. The arterial side of the aneurysm appears to have developed from the posterior portion of the circle of Willis in relation to the posterior cerebral arteries.

In all recorded instances the circle of Willis developed abnormally, with aberrant branches and with anomalous arterial stems.

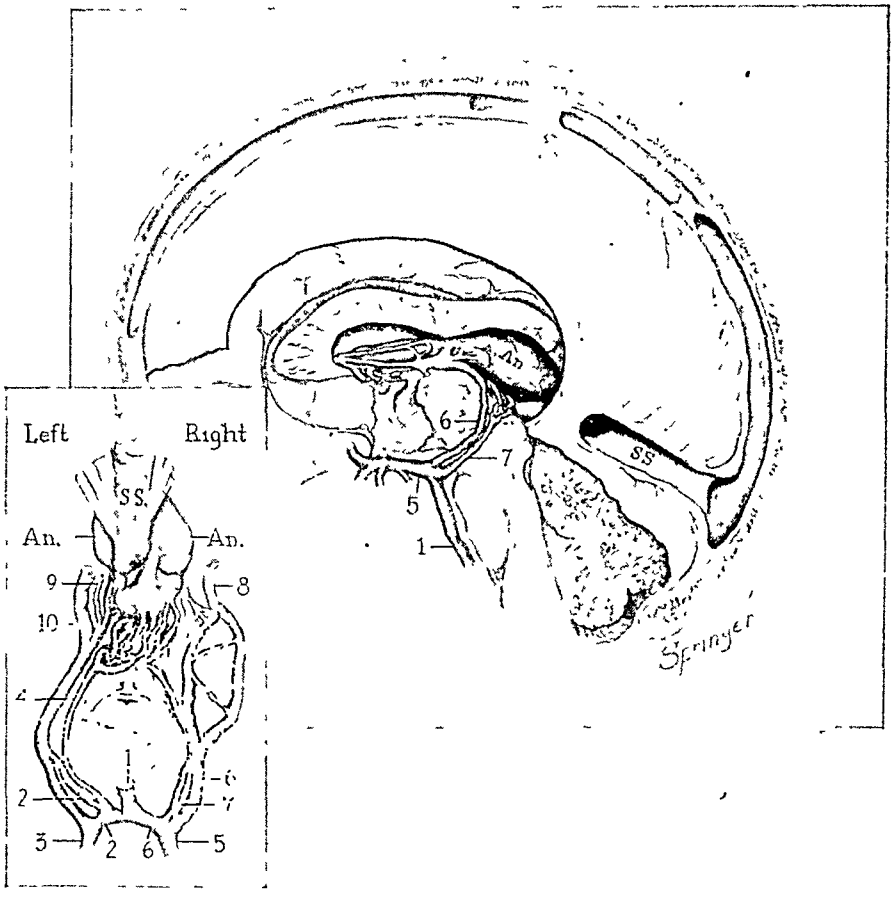



Fig. 5.—Parasagittal view, showing site of aneurysm and its relation to the falx, sinuses and ventricles. The insert is a drawing of the cross section of the brain stem and indicates the continuity of the vessels from the circle of Willis to the locations obtained in the horizontal section (fig. 3).

In all these cases the aneurysm was associated with internal hydrocephalus and headache. The problem has therefore arisen whether involvement of the great cerebral vein (Galen) is capable of producing internal hydrocephalus. The investigations of Bedford [3] seem to indicate that occlusion of this vein in the dog is incapable of producing internal hydrocephalus, despite scattered reports to the contrary. It seems more

3. Bedford, T. H. B.: The Great Vein of Galen and the Syndrome of Increased Intracranial Pressure, Brain **57**:1, 1934.

probable, therefore, that the hydrocephalus found in the recorded cases of aneurysm of the great cerebral vein was not the result of involvement of this vein itself but, rather, the effect of pressure on and occlusion of the aqueduct of Sylvius, though this is by no means definite. The cause of the associated hydrocephalus is not clear, but it remains a matter of great clinical interest that in all the recorded cases (Russell and Nevin; Jaeger; Alpers and Forster) the aneurysm has been associated with internal hydrocephalus.

SUMMARY

In the case of arteriovenous aneurysm of the great cerebral vein (Galen) recorded here, the venous side of the aneurysm was formed by the great cerebral vein, and the arterial supply came through the posterior cerebral and choroidal arteries. The aneurysm appears to have been congenital in origin. As in the 2 previously recorded cases, internal hydrocephalus was the only clinical feature of significance.

# INCIDENCE OF ADVANCED MATERNAL AGE IN MOTHERS OF ONE THOUSAND STATE HOSPITAL PATIENTS

HERBERT BARRY JR., M.D., PH.D.
BOSTON

Advanced maternal age has been shown to be related to a number of pathologic conditions in the offspring. While considerable attention has been devoted to a study of maternal age as related to such conditions as achondroplasia,[1] congenital cranial osteoporosis,[2] multiple births,[3] monstrosities [4] and abnormally large fetuses,[5] the maternal age at birth of children who subsequently become psychotic has received little emphasis. Gordon [6] reported 30 cases. His conclusion that "late marriage seems to favor the development of mental disorders in the offspring" seems rather sweeping on the basis of such a small series. Kawin [7] made the statement that parents of problem children tend to be slightly older than average. In general, however, the age of mothers at the time of birth of children who subsequently become psychotic has been almost universally ignored.

Several conditions involving the central nervous system have been shown to be related to maternal age. Of these, mongolism appears to have been investigated most thoroughly. Marston [8] showed in 1925 that 37 per cent of the mothers of mongolian idiots were 40 years of age or over at the birth of their defective offspring, as compared with 2.1 per cent of mothers over 40 in a control series. Since then, numerous investigators have confirmed and amplified his findings which relate mongolism to advanced maternal age, including Bleyer [9] and Penrose.[10] However, Rosanoff and Handy [11] and others emphasized the fact that young mothers may give birth to offspring with mongolism, and Southwick [12] has shown that births of mongolian idiots are not infrequently followed by the birth of a normal sibling. It is evident that advanced maternal age is in some manner related to mongolism, although other factors are more immediately involved in the pathogenesis of this condition.

## METHOD AND DATA

The present investigation is concerned with the age distribution of mothers at the time they gave birth to children who subsequently became psychotic. A series of 1,000 case histories were studied, for which the necessary data were available. The patients [13] were white persons representing first admissions to the New Jersey State Hospital, at Greystone Park, N. J., who were over 15 and under 40 years of age at the time of their admission to the hospital during the period 1930 to 1938. Patients over 40 were not included because of the relative paucity of information which is obtainable for older patients.[14] Data were secured from anamneses obtained by the social service department. These anamneses form part of the clinical record of the patients and are based on interviews with members of the patient's family, confirmed by other investigation when indicated. Anamneses at this hospital are complete and were obtained

From the Department of Neurology and Psychiatry of the Harvard Medical School, and the Department of Psychiatry of the Massachusetts General Hospital.

1. Bleyer, A.: Role of Advancing Maternal Age in Causing Achondroplasia, Am. J. Dis. Child. **58**:994-1000 (Nov.) 1939.

2. Reiss, O., and Boder, E.: Congenital Cranial Osteoporosis, Am. J. Dis. Child. **59**:931-1001 (May) 1940.

3. Guttmacher, A. F.: Analysis of 521 Cases of Twin Pregnancy, Am. J. Obst. & Gynec. **34**:76-84, 1937.

4. Murphy, D. P.: Congenital Malformations, Philadelphia, University of Pennsylvania Press, 1940.

5. Curtis, A. H.: Obstetrics and Gynecology, Philadelphia, W. B. Saunders Company, 1933, vol. 2.

6. Gordon, A.: Incidence of Psychotic Disorders in Individuals Whose Parents Married at an Advanced Age, M. Rec. **148**:109-112, 1938.

7. Kawin, E.: Children of Pre-School Age, Chicago, University of Chicago Press, 1934.

8. Marston, L. R.: Etiology of Mongolism, Psychol. Clin. **16**:135-140, 1925.

9. Bleyer, A.: Role of Advancing Maternal Age in Mongolism: A Study of 2,822 Cases, Proc. Am. A. Ment. Deficiency **61**:111-123, 1937.

10. Penrose, L. S.: Maternal Age, Order of Birth, and Developmental Anomalies, J. Ment. Sc. **85**:1141-1150, 1939.

11. Rosanoff, A. J., and Handy, L. M.: Etiology of Mongolism with Special Reference to Its Occurrence in Twins, Am. J. Dis. Child. **48**:764-779 (Oct.) 1934.

12. Southwick, W. E.: Time and Stage in Development at Which Factors Operate to Produce Mongolism, Am. J. Dis. Child. **57**:68-89 (Jan.) 1939.

13. Dr. Marcus A. Curry made the case histories available.

14. Barry, H., Jr., and Bousfield, W. A.: Incidence of Orphanhood Among Fifteen Hundred Psychotic Patients, J. Genet. Psychol. **50**:198-202, 1937.

by several different social workers, none of whom knew that the present investigation was contemplated. The results are presented in figure 1, which shows the distribution of maternal ages at the time of birth of these mental hospital patients. Maternal ages according to figures of

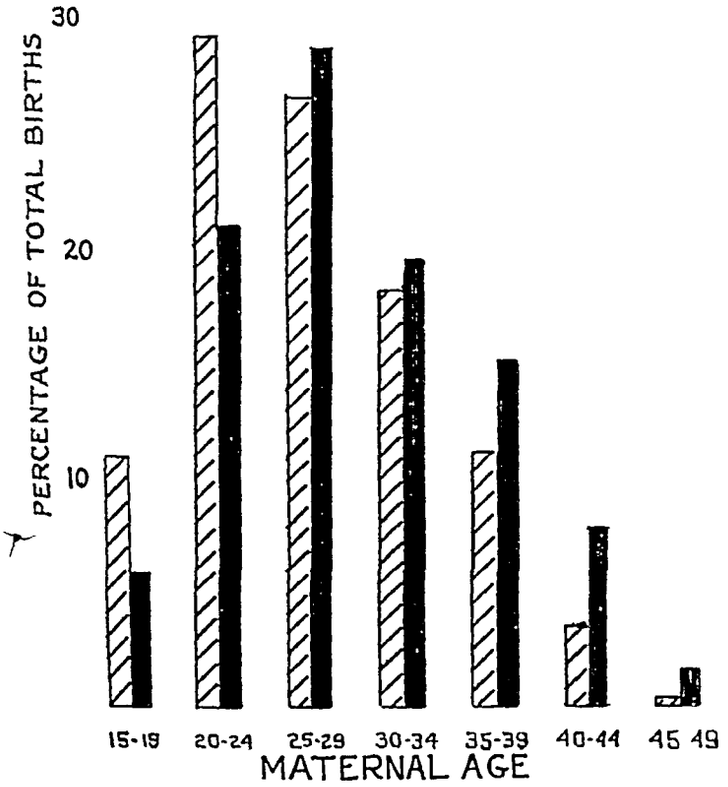



Fig. 1.—Percentage of births of normal and of psychotic persons plotted against the maternal age at birth. The solid rectangles represent psychotic patients; the cross-hatched rectangles, normal persons.

the United States Bureau of the Census, which include 7,000,000 births,[15] are presented as a control. The bar diagram indicates that the mothers of 1,000 state hospital patients are

TABLE 1.—*Ages of Mothers at Birth for Series of 1,000 Patients*

| Age of Mother | Number of Patients | | |
|---|---|---|---|
| | Male | Female | Total |
| 16-19 | 37 | 24 | 61 |
| 20-24 | 112 | 99 | 211 |
| 25-29 | 149 | 137 | 286 |
| 30-34 | 91 | 104 | 195 |
| 35-39 | 67 | 86 | 153 |
| 40-44 | 35 | 44 | 79 |
| 45 | 9 | 6 | 15 |
| Total | 500 | 500 | 1,000 |
| No information | 270 | 212 | 482 |

slightly, but quite consistently, older than the average. The differences are most apparent at the extremes: that is, for the oldest and youngest mothers. Table 1 gives data for maternal ages subdivided according to the sex of the patients. It will be noted that female patients in general show a slight tendency to have older mothers than male patients; in other words, the "shift to the right" in maternal age, which was noted for psychotic patients in figure 1, is accentuated in the case of females.

Although the number of patients for whom information on maternal age is lacking is large, there is no reason to suppose that the maternal ages for these patients would be materially lower than one for patients for whom data are available.

In table 2, the series is subdivided according to the clinical diagnosis. It will be seen that most of the subgroups are small, so that percentage differences would have little significance;

TABLE 2.—*Diagnoses for a Series of 1,000 Patients in a State Hospital*

| Diagnosis | Number of Patients | | | Patients with Mother Over 40 at Birth of Patient | |
|---|---|---|---|---|---|
| | Male | Female | Total | No. | Per Cent |
| Dementia precox | 348 | 236 | 584 | 53 | 9 |
| Manic-depressive psychosis | 37 | 135 | 172 | 18 | 11 |
| Psychoses with mental deficiency | 23 | 27 | 50 | 7 | * |
| Psychopathic personality | 20 | 19 | 39 | 1 | * |
| Syphilis of central nervous system | 20 | 5 | 25 | 1 | * |
| Psychoneurosis | 3 | 18 | 21 | 3 | * |
| Epilepsy | 11 | 11 | 22 | 4 | * |
| Epidemic encephalitis | 13 | 5 | 18 | 3 | * |
| Undiagnosed condition | 8 | 10 | 18 | 4 | * |
| Paranoid condition | 3 | 9 | 12 | 0 | * |
| Alcoholic psychosis | 9 | 0 | 9 | 0 | * |
| Postpartum psychosis | 0 | 5 | 5 | 0 | * |
| All other psychoses | 5 | 20 | 25 | 0 | * |
| Total | 500 | 500 | 1,000 | 94 | |

* Number of patients in subgroups is so small as to make percentage comparisons unreliable.

these differences have, therefore, not been computed except for the larger groups. Even with manic-depressive psychoses a difference of 2 cases could decrease the percentage of mothers over 40 from 11 to 9 per cent. The series includes few patients whose psychosis was diagnosed as paranoid or alcoholic, owing to the preponderance of younger patients in this series.

As a further basis for comparison, the data for a group of psychoneurotic patients from the psychiatric outpatient department of the Massachusetts General Hospital were analyzed in the same way. Data were obtained for 222 patients, aged 12 to 25, whose disorders had been diagnosed as psychoneuroses or as behavior problems. Of this group, only 8, or 3.6 per cent, had mothers who were over 40 at the time the patient was born. This percentage is substantially lower than the comparable figure of 9.4 per cent for psychotic patients; it is approximately the same as the figure of 3.9 per cent for the population of the United States. While

15. Cited by Bleyer.[1]

findings based on 200 cases are at most suggestive, these figures do not indicate that maternal ages are increased for psychoneurotic patients.

A similar incidence was obtained for another group of psychoneurotic patients at the Riggs Foundation, Stockbridge, Mass. Data were made available through the courtesy of Dr. C. N. Kimberly. Out of 73 patients, only 3 had mothers who were 40 or over at the time the patients were born. Although the patients in this series represent, for the most part, a superior socioeconomic status, maternal ages were comparable to figures for normal persons or to those for psychoneurotic patients studied at the Massachusetts General Hospital. Because the series is not large, percentages have not been computed.

TABLE 3.—*Mortality Rates for Mothers of Psychotic Patients According to Maternal Age at Birth of Patient*

| Age of Mother When Patient Was Born | Number of Patients: Mother Died When Patient Was Aged 0-19 | 20+ | Mother Living | Total Number of Patients | Per Cent of Maternal Deaths, Patient 0-19 Yr. Old |
|---|---|---|---|---|---|
| 15-19 | 8 | 7 | 46 | 61 | 13.1 |
| 20-24 | 31 | 18 | 162 | 211 | 14.7 |
| 24-29 | 56 | 30 | 200 | 286 | 19.6 |
| 30-34 | 38 | 19 | 138 | 195 | 19.5 |
| 35-39 | 28 | 30 | 95 | 153 | 18.3 |
| 40+ | 15 | 22 | 57 | 94 | 15.9 |
| Not stated | 128 | | 259 | 382 | Not stated |
| No data as to whether mother living or dead | | | | 100 | |

Table 3 indicates the mortality rates for mothers of psychotic patients, subdivided according to maternal age at the time of the patient's birth. Only 15.6 per cent of the mothers over 40 had died within twenty years, as compared with an expected mortality rate of 21.3 per cent. However, 13.1 per cent of the mothers under 20 died within twenty years, although the expected mortality was only 6.4 per cent.

The relationships which have been presented in table 3 are reproduced graphically in figure 2, which furnishes a comparison of actual and expected deaths among mothers of psychotic patients. Data for mortality expectation, by age groups, are computed on the basis of the life tables for white males and white females in the United States, 1929 to 1931.[15a]

Although the purpose of this paper is to indicate the age distribution of mothers of psychotic patients, the discussion would hardly be complete without some mention of heredity. One of the difficulties in evaluating the influence of heredity in mental disease is the establishment of satisfactory criteria as to what constitutes psychiatric abnormality in a parent. Since this paper is not concerned with the problem of heredity per se, any patient for whom there is a history of nervousness, irritability, mental illness, suicide, drunkenness, epilepsy, alcoholism or other evidence of psychiatric disturbance in

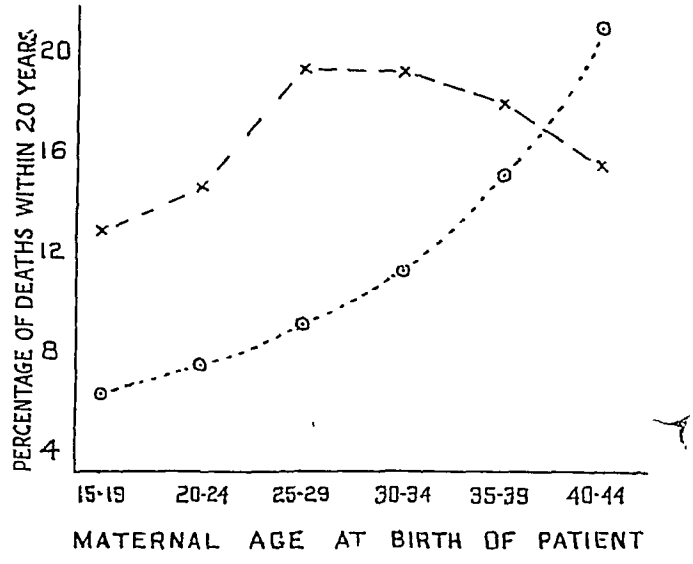



Fig. 2.—Mortality rates for mothers of psychotic patients distributed according to maternal age at time of patient's birth, as compared with the mortality expectation computed on the basis of the figures of the United States Bureau of the Census.[15]

either or both parents is taken to have a positive family history. While this criterion is admittedly indefinite and lacking in precision as a measure of genetic psychiatric abnormality, and though it includes only disorders reported for parents of patients, it may be useful as a relative measure

TABLE 4.—*Incidence of Nervous Instability in Parents of Psychotic Patients*

| Age of Mother at Birth of Patient | Cases of Parental Instability Reported | Cases in Which No Parental Instability Was Reported | Per Cent of Parental Instability |
|---|---|---|---|
| 15-19 | 21 | 40 | 34.4 |
| 20-24 | 64 | 149 | 30.0 |
| 25-29 | 85 | 199 | 29.9 |
| 30-34 | 52 | 143 | 26.6 |
| 35-39 | 36 | 117 | 23.5 |
| 40+ | 24 | 70 | 25.5 |
| Total | 282 | 718 | 28.2 |

of parental abnormality in patients with elderly and young mothers, respectively. The results are presented in table 4.

It is evident that if the relatives of psychotic patients who are considered for heredity were to include grandparents, nieces and cousins, the percentages of patients with a positive "heredity" would be materially higher than the figure just cited. On the other hand, if more rigorous

15a. Dublin, L. I., and Lotka, A. J.: Length of Life: A Study of the Life Table, New York, The Ronald Press Co., 1936, pp. 14-17.

criteria are employed, and the observations are limited to mothers alone, the percentages will be relatively small. For the patients of this series, 3.6 per cent of 1,000 mothers for whom parental ages were available and 9 per cent of 419 mothers for whom parental ages were unobtainable had a clearcut history of psychosis. The average incidence of psychoses for 1,419 mothers was 5.2 per cent. For 62 additional mothers no information whatever could be obtained; it seems likely that the percentage of psychoses would be higher for these persons. If this were true, the final figure for maternal psychoses might approach the value of 9 per cent reported by Bleuler [16] for 100 schizophrenic patients. Evidently, any evaluation of heredity must depend so much on the methods used and the type of cases selected that any further discussion of the topic is beyond the scope of this paper. It is sufficient to point out that on the basis of the data presented, maternal age and parental instability are not related to each other, though each of these factors evidently is related to psychoses in the offspring. In other words, maternal age is independent of parental instability, just as it was found to be independent of early death of the mother, for this group of psychotic patients.

Since there is evidence that maternal age and bereavement are independent variables and that maternal age and parental instability are also independent of each other, the relationship between bereavement and parental instability becomes of interest. Of 282 patients for whom parental instability is reported, 49, or 17.4 per cent, experienced the death of their mothers by the age of 19 years. Of 718 patients without report of parental instability, 131, or 18.2 per cent, experienced the death of their mothers by 19 years of age. While it seems doubtful that the maternal mortality rate would be higher for those without parental instability, and while a more probable explanation is that parental instability is less likely to be reported when the mother has been dead for some time, the figures are of interest. They indicate that for this series of 1,000 patients there are three groups of parental situations reported, with relatively little overlap: parental instability, 28.2 per cent; maternal bereavement, 17 per cent, and advanced maternal age, 9.4 per cent. All told, these three categories include 469 patients, or 46.9 per cent, of the entire series of patients for whom detailed information is available.

16. Bleuler, J.: A Contribution to the Problem of Heredity Among Schizophrenics, J. Nerv. & Ment. Dis. **74**:393-467, 1931.

## COMMENT

Three points stand out as a result of this investigation. First is the large number of patients (94, or 9.4 per cent) whose mothers were over 40 years of age when the patients were born. Second is the large number of patients (174, or 17.4 per cent) whose mothers died before the patients were 20 years of age. Third is the paradoxic finding that the death rate was relatively higher for the younger mothers than for the older ones. Since the overlap between the first two categories is small, over a quarter of the entire series had mothers who may be said to have been old when the patients were born or who died prematurely.

It is interesting that the "shift to the right" of maternal age for psychotic patients is more pronounced than that reported for patients with achondroplasia by Bleyer [1] or for patients with congenital malformations by Murphy.[4] Moreover, the present series is larger than that of either of these writers, who nevertheless felt that their results, based on 303 and 607 cases respectively, were significant. By the same token, it is obvious that maternal age per se is unlikely to produce any specific effect on the offspring. Since it is represented in such diverse conditions as monstrosities, achondroplasia and psychoses, the ultimate cause of all these disorders must be sought elsewhere. In psychoses, as in the other conditions cited, advanced maternal age can be at most a predisposing or related factor.

With respect to the statistical treatment of results in this and in other studies cited, a word of caution is in order. There have been remarkable changes in the birth rates, as well as the death rates, during the past twenty years. In many cases, the total variation within a relatively short period has been more than 50 per cent.[17] For this reason, the conventional formulas for "reliability" are of doubtful value. Moreover, the composition of any community does not remain constant. Vital statistics are thus subject to change, as the populations which they represent are in a state of flux. For example, Pearl [18] and others have reported census figures showing that maternal ages were higher for foreign-born mothers than for mothers born in the United States. A statistical bulletin for the Metropolitan Life Insurance Company [19]

17. Mortality Improving More Rapidly Among Women, Statist. Bull. Metrop. Life Ins. Co. **21**:4-7, 1940.

18. Pearl, R.: Variation in Parity of Women Bearing Children in the U. S. Birth Registration Area in 1930, Human Biol. **9**:65-98, 1937.

19. Fertility of Foreign Born Women Thirty Per Cent Greater Than Native Born, Statist. Bull. Metrop. Life Ins. Co. **12**:6, 1931.

indicates that there have been marked fluctuations in the percentage of children born to older mothers during the past twenty years. During this interval the birth rate for native-born mothers over 40 years of age has been halved. For foreign born mothers, it has dropped to less than one third. It is hardly necessary to point out that a computation of probable errors for every group might be grossly misleading, unless the groups to be compared were born at substantially the same time as the original group, and, furthermore, unless the percentages of native-born and foreign-born mothers were similar. Instead of computing coefficients of reliability (which are, strictly speaking, valid only in terms of the population studied), I am, therefore, contrasting the percentage of mothers over 40 for my series of mental hospital patients with the percentage of older mothers for several other groups. This comparison is given in table 5.

TABLE 5.—*Percentages of Births at Maternal Age of over 40 in Present Series and in Series of Normal Persons Reported by Other Investigators*

| Investigator | Cases | Place | Per Cent of Total Births in Which Mother Was 40 or Over |
|---|---|---|---|
| Anderson * | 2,373 | Cincinnati | 1.8 (single births; live born) |
| Marston [5] | 2,000 | ..... | 2.1 |
| Murphy [4] | 1,584 | Philadelphia | 2.0 (normal children) |
| Guttmacher [3] | 9,589 | Baltimore | 2.4 (all births) |
| Census figures | | United States | 3.88 |
| Present study | 1,000 psychotic patients | | 9.4 |

* Anderson, N. A.; Brown, E. W., and Lyons, R. A.: Causes of Prematurity, Am. J. Dis. Child. **61**: 72-87 (Jan.) 1941.

It will be noted that the percentage of mothers who were over 40 at the time they gave birth to a living child varies considerably among the normal groups, for reasons previously stated, but that it is much higher for the psychotic patients than for any of the normal groups reported. Of course, any statistical study cannot be accepted as final until it has withstood the test of independent confirmation. However, the evidence which is available indicates an excessive number of older mothers for mental hospital patients.

The second finding, namely, that many patients had experienced the death of their mothers during childhood, has been noted previously.[20] This finding has received some degree of confirmation in a paper by Rosenzweig and Bray.[21] Although these authors emphasize paternal mortality and are primarily concerned with schizophrenia, they present data which indicate that 7.2 per cent of their entire group of psychotic patients experienced the death of their mothers before they were 19, as compared with 2.5 per cent of a control group of normal persons. Both these figures seem low and might be increased if data had been available for all their subjects. Again, one sees the rather wide variation in percentages noted by different authors, which further emphasizes the need for caution in evaluating statistical findings.

The relation between psychosis and maternal mortality, as previously noted, might be interpreted in several ways: 1. Death of the mother might result in eventual psychosis in the offspring as a consequence of emotional trauma. 2. Death of the mother might result in a deterioration of the physical and emotional environment of the children. 3. An explanation might be invoked on a freudian basis in terms of disrupted family constellations and emotional tensions. 4. The relation might be incidental to some more immediate factor, such as the age of the mother (or even the age of the father). 5. Death of the mother might be evidence of deficient biologic stamina. This defect, if inherited by the children, might have as one manifestation the development of a psychosis.

The last possibility is consistent with the position taken by a number of investigators. Simms has written concerning a function which he designated as Q. This, Simms [22] asserted to be a measure of senile debility, both physical and mental, which also predisposes to a high death rate. He stated that superficial characteristics, such as condition of the hair and skin, are unsatisfactory criteria of senility. Indexes of unemployment and mortality rates he considered far more significant, according to mathematical equations which he worked out. Without passing on the validity of the equations which he proposed, it seems possible that mothers who died while in their twenties or thirties might be, *pari passu,* lacking in robustness or ruggedness, as in many cases they succumb to illnesses which are not fatal to a majority of women. In this connection, it is worth noting that the highest relative death rates for mothers of 1,000 mental hospital patients were among the younger mothers. Certainly, two phenomena noted for

20. Barry, H., Jr.: Study of Bereavement: An Approach to Problems in Mental Disease, Am. J. Orthopsychiat. **9**:355-359, 1939.

21. Rosenzweig, S., and Bray, D.: Sibling Deaths in Anamneses of Schizophrenic Patients, Arch. Neurol. & Psychiat. **49**:71-92 (Jan.) 1943.

22. Simms, H. S.: Physiological Alterations as the Cause of Senile Debility and Senile Mortality, Science **91**:7-9, 1940.

this group of psychotic patients—(1) a high rate of maternal bereavement, and (2) a disproportionate number of older mothers—might both be evidence of some biologic deficiency. However, any defect of these older mothers appears to have involved, primarily, their capacity to produce normal offspring, since their longevity compares favorably with normal persons or with younger mothers of psychotic patients.

A somewhat similar formulation which could account for both increased maternal age and increased mortality in mothers of psychotic patients has been discussed by Myerson[23] under the name "blastophoria." This makes use of a concept advocated by Adami[24] to the effect that germ plasm may be injured by environmental factors. Such injury has been demonstrated experimentally in animals by Stockard[25] and others. These investigators have shown that various forms of injury to the germinal epithelium may be antecedent to the appearance of defective offspring. It is, of course, possible that the degeneracy noted might be due to interference with normal embryonic development as a result of regressive changes either in the uterus or in the maternal blood stream, following debility or disease of the maternal organism.

While the foregoing discussion might apply to any of the disorders related to increasing maternal age, some progress has been made in tracing more specific relations between maternal age and two of the conditions previously noted. First, and most striking, is the discovery of the pathogenesis of erythroblastosis fetalis.[26] Since sensitization of the mother to the Rh factor normally occurs during pregnancy, a woman who has had numerous pregnancies is more likely to be sensitized; such a woman is also likely to be older. In this instance, the association between maternal age and erythroblastosis is apparently indirect. Another condition in which the relation between maternal age and a disease of the offspring is being formulated in terms of more specific pathogenic factors is mongolism. Benda[27] has postulated "noxious agents within the maternal organism" as being responsible for mongolism. These factors are supposedly related to endocrine disturbance within the mother. While his theories do not have the same degree of experimental confirmation as those which explained erythroblastosis fetalis, this is a stimulating approach. If his theory is correct, mongolism, as well as erythroblastosis, can be said to result from biochemical changes in the maternal organism which develop or become accentuated with age.

A number of incidental findings of this study are beyond the scope of the present paper. There is some evidence that fathers of patients at Greystone Park may have an older age distribution than fathers of normal persons (United States Census figures). It is possible that debility might operate through the paternal, as well as the maternal, germ plasm. In view of the well known hazards of statistical argument, it is hoped that these, as well as the major, findings presented in this report may be considered as preliminary—pending adequate confirmation.

## SUMMARY AND CONCLUSIONS

1. Of 1,000 patients at a state hospital, 94 (9.4 per cent) had mothers who were over 40 years of age at the time of the patient's birth.

2. In the same series of patients, 174 (17.4 per cent) had mothers who died before the patients were 20 years old.

3. Paradoxically, there was a high death rate among the younger mothers, with a relatively low mortality rate among the mothers over 40 years of age.

4. In a preliminary series of psychoneurotic patients, the percentage of older mothers (3.6) was within normal limits.

23. Myerson, A.: Inheritance of Mental Diseases, Baltimore, Williams & Wilkins Company, 1925, p. 286.

24. Adami, J. G.: Medical Contributions to Study of Evolution, New York, MacMillan and Company, 1918; cited by Myerson.[23]

25. Stockard, C. R.: Physical Basis of Personality, New York, W. W. Norton & Company, Inc., 1931.

26. Levine, P.; Burnham, L.; Katzin, E., and Vogel, P.: Role of Iso-Immunization in the Pathogenesis of Erythroblastosis Fetalis, Am. J. Obst. & Gynec. **42**: 925-937, 1941.

27. Benda, C. E.: Endocrine Aspects of Mongolism, J. Clin. Endocrinol. **2**:737-748, 1942.

# MÉNIÈRE'S SYNDROME

## COMPARISON OF RESULTS OF MEDICAL AND SURGICAL TREATMENT

MILES ATKINSON, M.D., F.R.C.S.
NEW YORK

The variety of treatments advocated for Ménière's disease is sufficient proof that the mechanism producing the attacks is not yet completely understood. Nevertheless, since good results are claimed for all methods, it has seemed that it would at least be interesting, and might be instructive, to compare the methods on the basis of published results.

### MEDICAL TREATMENT

Table 1 shows the results claimed for various current medical treatments. All of these methods but one are predicated on clinical experiments made by their originators. Intravenous administration of histamine alone was a chance finding and is in that sense empiric. The usual criterion taken for success in treatment is relief of the attacks of vertigo. This varies rather widely in different series; but if the combined figures for relief and for marked improvement are taken, it is remarkable how closely the results coincide. In every series but one, more than 80 per cent of the patients were claimed to be greatly improved, the exception being the series of Walsh and Adson,[1] in which improvement was claimed to have been obtained in only 62 per cent with use of an accepted method not originated by the authors.

How can this rather unexpected finding be explained? The cynic may say that it is due to the predilection of a parent for his offspring—though, even so, it still seems strange that all the spectacles should be so uniformly tinted. The skeptic may suggest that the figures indicate not so much relief of vertigo as the natural tendency of the disease to remission, which notoriously makes computation of results difficult; but such prolonged remission or relief, though it may, and does, happen in individual instances, does not occur in 80 per cent of untreated patients. No doubt there is some error in all these figures due to this natural tendency of the disease to remission, but it may be called a constant variable. It could not well account for the great similarity in

TABLE 1.—*Results of Various Medical Treatments for Ménière's Syndrome*

| Author; Treatment | Period of Observation | Number of Cases | Relief of Vertigo | Improvement of Vertigo | Improvement of Deafness | Improvement of Tinnitus |
|---|---|---|---|---|---|---|
| Mygind and Dederding,[5] 1934 (salt-free diet and dehydration) | Up to 3 yr. | 157 | 43% | 52% (95%) | 17.4% | Not stated |
| Furstenberg,[6] 1934 (sodium-free diet plus ammonium chloride) | 3 mo. to 7 yr. | 35 | 57% | 26% (83%) | 9% | 51% |
| Walsh and Adson,[1] 1940 (low salt diet plus ammonium chloride or potassium nitrate) | Up to 4 yr. | 152 | 34% | 28% (62%) | 28% | "Essentially the same as deafness" |
| Talbott and Brown,[7] 1940 (high potassium diet) | 1 mo. to 16 mo. | 27 | 0% | 96% "No acute attacks" (96%) | Not stated | "Some" |
| Lillie, Horton and Thornell,[11] 1944 (histamine intravenously) | 1 mo. to 2 yr. | 25 | 60% "While at clinic" | 24% (84%) | 48% | 56% |
| Atkinson,[9] 1944 (nicotinic acid) | 6 mo. to 3 yr. | 110 | 38% | 46% (84%) | 23% | 52% |
| Atkinson (unpublished) (histamine desensitization) | 4 yr. | 21 | 76% | 14% (90%) | 24% | 38% |

This paper was read at a joint meeting of the New York Academy of Medicine, Section of Neurology and Psychiatry, and the New York Neurological Society, March 13, 1945.

From the Ear, Nose and Throat Service of the Third (New York University) Surgical Division, Bellevue Hospital, and the Department of Otorhinolaryngology, New York University College of Medicine.

1. Walsh, M. N., and Adson, A. W.: Ménière's Syndrome: Medical vs. Surgical Treatment, J. A. M. A. **114**:130 (Jan. 13) 1940.

the figures. There would seem to be two possible explanations. Either there is an unknown factor in the disease which has been overlooked by all the various investigators, or the pathologic process which produces the attack is such as could be influenced by each of these different measures, in its own particular way.

I do not want to speculate on a possible unknown factor, if there is one. Speculation plays too great a part in attempts to explain Ménière's syndrome as it is. The other possibility, that there is a common basic fault which is influenced by each of the current methods of treatment, seems a more plausible explanation. This basic fault could be an alteration in capillary permeability, which in cases of Ménière's syndrome involves particularly the capillaries of the stria vascularis in the labyrinth. This explanation has been advanced before by Brunner [2] and Portmann [3] and has in recent years received support from the histologic changes in a number of cases in which dilatation of the endolymphatic spaces has been shown (see Altmann and Fowler [4] for a complete review).

An increase in capillary permeability can be produced in one of two ways, either by anoxia from a diminished blood supply, which impairs the function of the capillary wall, or by sensitization to some foreign protein or chemical, as occurs classically in allergy, with the same result. In either case, seepage of serum takes place into the tissues, in the labyrinth into the endolymphphatic spaces. If this theory is accepted, the various treatments advocated and the consistency of the results make sense. One method of treatment restricts fluid intake (Mygind and Dederding [5]), and thus there will be less fluid to seep through the damaged capillary walls; another produces dehydration by administration of large doses of ammonium chloride (Furstenberg [6]) with the same result; another seeks to alter the electrolyte balance (Talbott and Brown [7]); others combat anoxia by producing vasodilatation (histamine,[8] nicotinic acid [9]) and so improve the function of the capillary wall; another produces desensitization in appropriate cases (histamine desensitization [10]) and seeks in this way to prevent and overcome the damage to the capillaries. This explanation is offered in no dogmatic spirit. It does, however, fit the known facts.

As to the merits of the various methods, I naturally favor my own. I find that I obtain results with them which I cannot obtain with the methods of others. This is probably in part because I have had more experience with them than with the others; in part also, no doubt, because I pursue them with more enthusiasm, but mainly, I am sure, because I attempt, however inadequately as yet, to group patients according to the cause of the syndrome and to treat them accordingly. One does well to remember that Ménière's syndrome *is* a syndrome and that its characteristic manifestations can be produced by several initiating factors. I find that the disease in patients who have been unsuccessfully treated with other methods can often be controlled when they are correctly grouped—but then, obviously, I see only my colleagues' failures, and not their successes, as they no doubt see mine. For instance, Dr. Madeleine Brown wrote me recently that she "continues to get good results in treatment of the acute form with potassium chloride." Yet I have several patients, some from Boston and environs, who have been treated with potassium chloride adequately and persistently with no, or only initial, success. I personally have tried conscientiously in the past all the methods enumerated in table 1, admittedly in small groups of patients only. I cannot approach the success which their authors claim for them. Indeed, only on rare occasions have I had any success at all. But I know that others say the same about my methods; so perhaps I have not been conscientious enough or persistent enough. Or perhaps each method has virtue in particular cases, and we physicians have not learnt enough to select cases correctly. But whatever may be the ex-

2. Brunner, H.: Die Pathologie und Therapie der vasomotorischen Erkrankungen des Innenohres, Wien. klin. Wchnschr. **38**:1235 (Nov. 12) 1925.

3. Portmann, G.: Vasomotor Affections of the Internal Ear, Ann. Otol., Rhin. & Laryng. **38**:69 (March) 1929.

4. Altmann, F., and Fowler, E. P., Jr.: Histological Findings in Ménière's Symptom Complex, Ann. Otol., Rhin. & Laryng. **52**:52 (March) 1943.

5. Mygind, S. H., and Dederding, D.: Diagnosis and Treatment of Ménière's Disease, Ann. Otol., Rhin. & Laryng. **47**:768 (Sept.) 1938.

6. Furstenberg, A. C.; Lashmet, F. H., and Lathrop, F.: Ménière's Symptom Complex: Medical Treatment, Ann. Otol., Rhin. & Laryng. **43**:1035 (Dec.) 1934.

7. Talbott, J. H., and Brown, M. R.: Ménière's Syndrome: Acid-Base Constituents of the Blood; Treatment with Potassium Chloride, J. A. M. A. **114**:125 (Jan. 13) 1940.

8. Shelden, C. H., and Horton, B. T.: Treatment of Ménière's Disease with Histamine Administered Intravenously, Proc. Staff Meet., Mayo Clin. **15**:17 (Jan. 10) 1940.

9. Atkinson, M.: Ménière's Syndrome: Results of Treatment with Nicotinic Acid in the Vasoconstrictor Group, Arch. Otolaryng. **40**:101 (Aug.) 1944.

10. Atkinson, M.: Histamine in the Treatment of Ménière's Syndrome: An Appraisal, J. A. M. A. **119**:4 (May 2) 1942.

planation, what is evident is that it is seldom that the vertigo cannot be controlled with medical measures of one sort or another.

Control of deafness and tinnitus is a different story. Tinnitus can be notably improved in some 50 per cent of all cases, and in a few it can be entirely relieved. Hearing, however, can be improved only in some 20 per cent of cases, and then not usually markedly, though in a small series Lillie and his collaborators,[11] using intravenous injections of histamine, obtained improvement in 48 per cent of cases. Usually the most that can be done is to hold the line and prevent a further loss. Damage done to hearing seldom can be undone.

great magnitude, for which good results are claimed by those that use it.[12] Portmann himself has never published any figures, as far as I can find out, but Waltner's [12b] are from his clinic. The concept is logical, but the operation has never "caught on."

Removal of foci of infection [13] is predicated on the theory that attacks of the Ménière syndrome are due to "toxic neuritis" of the eighth cranial nerve. The "focus" is usually to be found in some easily accessible organ, like the tonsil, the nasal sinuses or the teeth, and less often in an organ more difficult of attainment, like the gallbladder or the appendix. If one were to judge solely from the published figures, one would have to agree

TABLE 2.—*Results of Various Surgical Treatments for Ménière's Syndrome*

| | Period of Observation | Number of Cases | Relief of Vertigo | Improvement of Vertigo | Improvement of Deafness | Improvement of Tinnitus |
|---|---|---|---|---|---|---|
| Operations on Eighth Nerve | | | | | | |
| Coleman and Lyerly,[15] 1933 | Not stated | 10 | 100% | .... | 0% | 100% |
| | | | | 100% | | |
| Crowe,[14] 1938 | Average 2.2 yr. | 72 | 100% | .... | 19.5% | Not stated |
| | | | | 100% | | |
| Walsh and Adson,[1] 1940 | Not stated | 20 | 65% | 30% | Not stated | Not stated |
| | | | | 95% | | |
| Operations on Labyrinth | | | | | | |
| Mollison,[16] 1939 | Not stated | 50 | 74% | 16% | Not stated | Not stated |
| | | | | 90% | | |
| Cawthorne and Hallpike,[17] 1943 | Up to 2 yr. | 50 | .... | 92% | 22% | 44% |
| | | | | 92% | | |
| Day [19] 1944 | 1-3 yr. | 8 | 75% | .... | 12.5% | 75% |
| | | | | 75% | | |
| Portmann Operation on Saccus Endolymphaticus | | | | | | |
| Woodman,[12a] 1939 | Not stated | 11 | 73% | 9% | 5.5% | 3% |
| | | | | 82% | | |
| Waltner,[12b] 1940 | Not stated | 11 | 72% | 9% | 45% | 18% |
| | | | | 81% | | |
| Removal of Foci of Infection | | | | | | |
| Wright,[13] 1940 | More than 6 mo. | 84 | 83% | 5% | 70% | 59% |
| | | | | 88% | | |

## SURGICAL TREATMENT

The various operations practiced fall essentially into two groups. One, the less common, consists of procedures predicated, like medical treatment, on a theory of causation; the other, and the more common, consists of operations of destruction on some part of the vestibular tract (table 2).

1. To take the less common group first, the Portmann operation seeks to overcome the increased production of endolymph by draining the labyrinth through the saccus endolymphaticus in the posterior fossa. It is an operation of no

that without a doubt this procedure is the answer to the problem both of causation and of treatment. Unfortunately, Wright stands a lone figure. His findings are against the weight of the evidence. Other workers in the field find no such prevalence of local infections (Crowe [14]).

11. Lillie, H. I.; Horton, B. F., and Thornell, W. C.: Ménière's Symptom Complex: Observations on Hearing of Patients Treated with Histamine, Ann. Otol., Rhin. & Laryng. **53**:717 (Dec.) 1944.

12. (*a*) Woodman, E. M.: The Position of the Portmann Operation in Relation to Labyrinthine Vertigo, Proc. Roy. Soc. Med. **32**:1642 (Oct.) 1939. (*b*) Waltner, J.: Le blocage du sac endolymphatique et l'opération de Portmann, Rev. de laryng. **61**:1 (Jan.) 1940.

13. Wright, A. J.: Further Clinical Observations on the Nature and Treatment of Ménière's Disease, Proc. Roy. Soc. Med. **33**:459 (June) 1940.

14. Crowe, S. J.: Ménière's Disease: A Study Based on Examinations Made Before and After an Intracranial Division of the Vestibular Nerve, Medicine **17**: 1 (Feb.) 1938.

They do not obtain the results from removal of tonsils, teeth and so forth that Wright has claimed. I myself, as a matter of routine, always look for a focus of infection. I scarcely ever find one. Nor have I ever found that removal of such a focus relieved the patient of his attacks, at least more than temporarily, in the way that tonsillectomy "cures" rheumatoid arthritis for a month or so; and I see many patients that have had this or that done to them before they reach me. If I have expatiated rather lengthily on this matter, it is because I believe that we physicians should set our faces against these nibbling operations, which in the general experience profit the patient not at all.

2. To turn now to the operations which are more commonly practiced, the operations of destruction, a different principle is encountered. Whereas medical treatment and the former group of operations attempt to overcome the assumed cause, these operations are concerned solely with preventing the effect. By dividing the conducting pathway, the vestibular nerve, or destroying the end organ in the labyrinth, they seek to prevent the stimulus from becoming effective. They do nothing to affect the stimulus itself. One may liken the state of affairs to an unwanted telephone conversation. These operations cut the wire or destroy the instrument so that the voice does not come through; they do not get rid of the speaker.

What, then, may be expected of surgical intervention? As far as section of the eighth nerve is concerned, the operation should theoretically be 100 per cent successful as regards relief of vertigo. So in practice it seems to be (Crowe,[14] Coleman and Lyerly[15] and Ray,[16] unreported series of 40 cases), provided—and the proviso is important—the diagnosis is correct and the operation complete.

If the diagnosis is incorrect, and if operation is performed in cases of paroxysmal vertigo not the result of labyrinthine disturbance, there will be distressing failures. I have in my records cases in which nerve section has been performed for paroxysmal vertigo which did not fulfil the criteria demanded for a diagnosis of Ménière's syndrome, and in which the condition was made not better but worse. Some of these cases come from a series in which 100 per cent success in surgical relief of vertigo was claimed. If the operation is incomplete failure again will occur, for which reason some surgeons (Ray) are tending to return to the older operation of total section of the nerve, holding it preferable to partial section, even though absolute deafness in the ear operated on is the price that must be paid. As to the other symptoms, hearing is seldom affected by section except for the worse, but tinnitus, strangely, is occasionally diminished, and even in rare instances relieved entirely, by section of the eighth nerve, either partial or complete.

Operations on the labyrinth differ somewhat in their results, depending on the particular procedure employed. The technics used are essentially of two kinds, one conservative and the other destructive. The first consists merely in opening the labyrinth, usually through the external semicircular canal (Cawthorne and Hallpike[17]); the second, in addition, employs injections of alcohol (Mollison[18]) or uses a coagulating current to destroy the whole, or a selected part, of the end organ (Day[19]). In general, relief of vertigo is less certain with this type of operation than with section of the eighth nerve; improvement in tinnitus and hearing, more usual with the conservative type. It is possible that, as more experience is gained with this type of operation and with the technical difficulties involved, it may come to supplant section as the the operation of choice. It is the more logical procedure.

But no matter what type of operation is to be performed, it is the general opinion of neurosurgeons, as well as otologists, that surgical intervention is to be regarded as the final resource. Not until medical treatment has been tried and failed should surgical therapy be advocated, except in special circumstances in which time is of primary importance and the diagnosis is without a doubt. Surgical measures can never offer as good results as can medical treatment at its best, which can on occasion procure a return to normal[9]; the results of surgical treatment are, however, more consistent and more rapid with regard to relief of vertigo.

## CONCLUSION

The present position may be summarized as follows: Medical treatment can relieve or con-

15. Coleman, C. C., and Lyerly, J. G.: Ménière's Disease: Diagnosis and Treatment, Arch. Neurol. & Psychiat. **29**:522 (March) 1933.

16. Ray, B. S.: Unpublished results.

17. Cawthorne, T. E., and Hallpike, C. S.: Some Recent Work on the Investigation and Treatment of "Ménière's" Disease, Proc. Roy. Soc. Med. (Sect. Otol.) **36**:21 (Aug.) 1943.

18. Mollison, W. M.: Surgical Treatment of Vertigo by Opening the External Semicircular Canal and Injecting Alcohol, Acta oto-laryng. **27**:222, 1939.

19. Day, K. M.: Surgery of the Labyrinth for Ménière's Disease, Tr. Am. Acad. Ophth. (1943) **48**: 221 (March-April) 1944.

trol attacks of vertigo in some 80 per cent of cases; it can offer relief from or substantial improvement in tinnitus, a symptom which is often as distressing as vertigo, in some 50 per cent of cases; it can improve hearing to some extent in approximately 20 per cent of cases. Surgical treatment is to be regarded as a last resource when medical treatment has failed, but in selected cases it can be relied on to abolish vertigo; more should not be expected of it. It should always be remembered that operation is not entirely devoid of risk and that its results are irretrievable. Ménière's syndrome of itself is a benign condition, however distressing. It was not until the surgeons entered the arena that postmortem material became available for histologic study.

127 East Seventieth Street.

# ELECTROENCEPHALOGRAPHIC LOCALIZATION AND DIFFERENTIATION OF LESIONS OF FRONTAL LOBES

## PATHOLOGIC CONFIRMATION

CAPTAIN CHARLES LeVANT YEAGER *
MEDICAL CORPS, ARMY OF THE UNITED STATES
AND
SARAH LUSE, A.B.
Technical Assistant, Mayo Clinic
ROCHESTER, MINN.

In dealing with intracranial lesions involving only the frontal lobes of the brain, the physician often is confronted with a paucity of neurologic evidence on which to base his judgment. Electroencephalography recently has been introduced as a procedure which, because of its applicability, appears to provide a partial solution of this problem. Although the electroencephalogram is utilized in the localization of lesions situated in various parts of the brain, this study is limited to those of the frontal lobes.

The question has arisen whether there are any characteristics in the abnormal electric activity of the cerebral cortex that would correlate with the underlying pathologic processes. A partial answer to this question is presented in this paper.

Since a detailed discussion of the literature is not included, the excellent reviews of Jasper,[1] Walter[2] and Gibbs and Gibbs[3] may be consulted. Walter[4] was the first to describe the accurate localization of cerebral tumors by means of the electroencephalogram as recorded from the surface of the scalp. He found slow random waves that were confined to the area of the head representing the site of the underlying tumor and called them delta waves. This term has been used to designate waves ranging from 1 to 7 cycles per second.[5]

### TECHNIC

Electroencephalographic tracings were made with a four channel Grass balanced amplifier and an ink-writer that records on a paper tape moving at the rate of 30 mm. per second. The electrodes, 5 mm. in diameter, are stamped out of lead solder and are attached to the input terminals of the amplifiers by means of fine copper wires. These electrodes are filled with saline jelly and are fastened to the cleansed scalp of the patient with collodion. They are placed 5 cm. from the midsagittal line over the prefrontal, motor, anterior parietal, posterior parietal and occipital areas. The occipital electrodes rest 1.5 cm. in front of the inion. Electrodes are placed in the same manner over the temporal regions about 7 cm. directly above each external auditory meatus. In order to do both monopolar and bipolar recording, an electrode is attached to the lobe of each ear, and these two electrodes are connected to serve as a single reference lead. The electrodes on the head then become the specific leads. Suboccipital leads are utilized to help in distinguishing lesions of the cerebellum from those of the frontal lobes.

The conditions of recording are standardized as nearly as possible. The patients are placed on a bed in a semidarkened and electrically shielded room. They are instructed to lie as quietly as possible, with the eyes closed, but to remain in a waking state. Any sudden change in appearance of the electric waves prompts the technician to speak to the patient in order to prevent his falling asleep or drifting into a semidream state—two important factors which can produce certain interfering abnormalities in the wave pattern.

### MATERIAL

This study is based on data concerning 100 consecutive patients, 67 men and 33 women, who had lesions of the frontal lobes of the brain. Each patient had a complete neurologic examination, including electroencephalographic recordings.[6] This series was selective

* At the time this study was made, Dr. Yeager was First Assistant in Neurology, at the Mayo Foundation.

This paper is an abridgment of a thesis submitted by Dr. Yeager to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Neurology and Psychiatry.

1. Jasper, H. H.: Electrical Signs of Cortical Activity, Psychol. Bull. **34**:411-481 (July) 1937.

2. Walter, W. G.: The Technique and Application of Electro-Encephalography, J. Neurol. & Psychiat. **1**: 359-385 (Oct.) 1938.

3. Gibbs, F. A., and Gibbs, E. L.: Atlas of Electroencephalography, Cambridge, Mass., Lew A. Cummings Co., 1941.

4. Walter, W. G.: The Location of Cerebral Tumours by Electro-Encephalography, Lancet **2**:305-308 (Aug. 8) 1936; The Electro-Encephalogram in Cases of Cerebral Tumour, Proc. Roy. Soc. Med. **30**:579-598 (March) 1937.

5. It is also proper to use the terminology of frequencies and potentials in referring to the various waves, although in this paper the original nomenclature has been retained to simplify description.

6. All electroencephalograms were read in the absence of any knowledge of the medical history or results of the neurologic examination of the patient. Usually the patient was not seen by the person who interpreted the record.

in that each lesion was confined to the frontal lobes, so far as it was possible to determine. Confirmation of all lesions was achieved either by surgical pathologic methods or by necropsy. Except for the aneurysms, all lesions in this series were verified microscopically.

In table 1 are indicated the types of lesions and the number of each type encountered.

TABLE 1.—*Types and Number of Lesions Encountered in 100 Cases of Lesions of the Frontal Lobe*

| Type of Lesion | Cases |
|---|---|
| Spongioblastoma multiforme | 31 |
| Meningioma | 26 |
| Unclassified glioma | 7 |
| Neoplastic metastasis | 7 |
| Hemorrhage and infarct | 6 |
| Astrocytoma | 6 |
| Aneurysm | 3 |
| Oligodendroblastoma | 3 |
| Abscess | 3 |
| Astroblastoma | 2 |
| Oligodendroglioma | 2 |
| Ependymoblastoma | 2 |
| Ependymoma | 1 |
| Osteoma | 1 |
| Total cases | 100 |

## RESULTS

Forty-two of the 100 persons studied were shown by surgical intervention to have lesions involving the left frontal lobe. Forty-seven had lesions involving the right frontal lobe. Eleven had lesions involving both frontal lobes.

Table 2 shows the site of the delta localization in each case in which a focus was present. In 2 cases the results of the electroencephalographic examinations were normal in the presence of tumors.

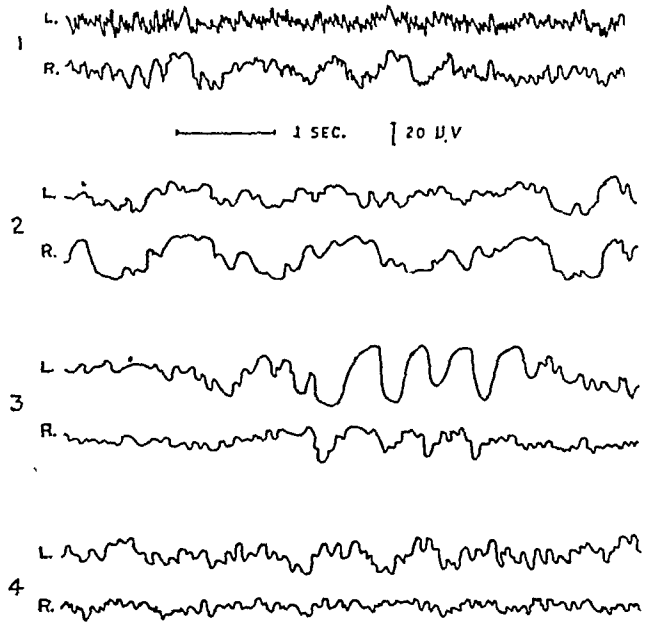
TABLE 2.—*Localization of Lesions as Indicated by Electroencephalograms*

| Interpretation of Electroencephalographic Recordings | Total No. | Correct Area | Wrong Side | Electroencephalogram Misleading | Unlocalized Activity |
|---|---|---|---|---|---|
| Bilateral frontal delta localization | 14 | 8* | .. | .. | .. |
| Unilateral delta localization | | | | | |
| Frontal | 35 | 34 | 1 | .. | .. |
| Frontotemporal | 31 | 30 | 1 | .. | .. |
| Frontotemporoparietal | 3 | 3 | .. | .. | .. |
| Frontoparietal | 1 | 1 | .. | .. | .. |
| Temporal | 3 | .. | .. | 3 | .. |
| Temperoparietal | 1 | .. | .. | 1 | .. |
| Parietal | 2 | .. | .. | 2 | .. |
| Temporo-occipital | 2 | .. | .. | 2 | .. |
| Occipital | 1 | .. | .. | 1 | .. |
| Generalized delta activity | 4 | .. | .. | .. | 4 |
| Normal electroencephalogram | 2 | .. | .. | .. | 2 |
| Indeterminate | 1 | .. | .. | .. | 1 |
| Total | 100 | 76 | 2 | 9 | 7 |

* In the remaining 6 cases the lesions were found at operation or necropsy to be unilateral, whereas our interpretation of the electroencephalogram had designated them as bilateral. Thus, these 6 cases do not represent either complete errors or complete successes and do not appear in either the "correct" or the "wrong" column.

The 100 electroencephalographic records were divided into three main groups. The first group was characterized by a relatively constant delta activity of from 3 to 6 cycles per second and of moderate potential (40 to 80 microvolts). The contour of the waves throughout the record presented considerable irregularity and sharpness. This delta activity was commonly confined to a single area as a rather circumscribed focus. When generalized delta activity was present, it was usually minimal and frequently was limited to one hemisphere. The occipital alpha rhythm was absent or reduced in amplitude. The frontal beta activity remained unaffected and at times seemed to be increased either on the side opposite that of the lesion or on both sides (figure).

Group 2 was characterized by an irregular, random, slow and smooth delta activity of high potential (50 to 150 microvolts), with a smooth




Electroencephalographic tracings taken from the frontal regions (*L*, left; *R*, right) in cases of the following lesions of the brains: (*1*) Meningioma of the right frontal lobe. The delta activity is moderately slow and well circumscribed, with fast beta activity superimposed on it. The beta activity is predominant on the opposite side (a common finding). (*2*) Spongioblastoma multiforme of the right frontal lobe. The frequency is slow and the amplitude high. Normal frequencies are absent on the side of the lesion. There is considerable delta activity on the side opposite the lesion. The general picture is that of a slow, smooth type of wave. This suggests severe damage. (*3*) Astrocytoma of the left frontal region, with a cyst filled with fluid. Note the rhythmic, high amplitude, sinusoidal chain of waves. They were frequently found with cystic lesions and with abscesses. (*4*) Old hemorrhage of the left frontal lobe. Note the low amplitude waves with considerable variation of frequency. In this case there are some spontaneous waves—both alpha and beta.

rounded, partially sinusoidal contour. Generalized delta activity was prevalent, and the beta rhythm of the frontomotor regions usually was abolished. There was a pronounced diminution or absence of the occipital alpha rhythm

on the side of the lesion. In most instances the electric activity of the opposite cerebral hemisphere was involved, with a partial decrease of the occipital alpha activity.

Group 3 included those records which are less easily described and classified. These records presented a more or less heterogeneous pattern, often described as ragged and choppy. The delta activity noted was of low potential and variable in frequency with superimposed alpha and beta activity. The spontaneous alpha and beta waves, whether superimposed or in areas free of delta activity, were sparse, of low potential and irregular in form.

In 19 (73 per cent) of the 26 cases of meningioma, the wave pattern was found to be in electroencephalographic group 1. In 6 cases (23 per cent), in all of which the tumor was shown microscopically to be of the malignant cellular type, the delta activity was in electroencephalographic group 2, and in 1 (4 per cent) it was in electroencephalographic group 3.

In the 1 case of osteoma of the frontal bone, pressing on the cerebral cortex, the delta activity had the characteristics of electroencephalographic group 1. This wave pattern resembled that seen with the meningiomas and may be explained by the similar cortical changes produced by meningiomas and osteomas.

In 43 (80 per cent) of the 54 cases of glioma the wave patterns were in electroencephalographic group 2; in 8 cases (15 per cent), in group 3, and 1 case (2 per cent), in group 1. Of the 2 remaining cases of glioma, a circumscribed epileptogenic focus of low potential in the motor area was present in 1, and asymmetry, with reduced alpha activity on the side of the lesion, in the other.

Of the 12 cases of non-neoplastic lesions of various types (hemorrhage, infarct, abscess and aneurysm), the wave patterns in 7 (58 per cent) were found to be in electroencephalographic group 3; in 2 cases (17 per cent), in group 1, and in 3 cases (25 per cent), in group 2.

In 5 (71 per cent) of the 7 instances of neoplastic metastasis the records were in electroencephalographic group 2, and in 2 (29 per cent), in group 3.

The pattern of the electroencephalograms in group 1 was found to be associated with meningiomas in the majority of cases, and the pattern in group 2 was identified with gliomas of all types (table 3). The intensity of the changes in the record depended in part on the nature and extent of the lesion. The changes were most pronounced in the presence of spongioblastoma multiforme. When the existing lesion contained cystic cavities, an additional wave pattern of high potential, sinusoidal waves of 2 to 3 cycles per second appearing in intermittent sequences was frequently found. The wave form characteristic of abscesses resembled closely the wave form characteristic of cystic lesions except for less obvious sinusoidal sequences. For the most part metastatic lesions produced electric patterns resembling those of gliomas. Vascular lesions presented a pattern similar to that seen in group 3.

In evaluating changes in the records according to these classifications, it should be emphasized that such groupings are arbitrary and may overlap, so that some of the characteristics of all the groups may be found in a single record.

The interpretation of each record depends on a number of variable factors. One should always consider the wide range of normal variations in the electroencephalogram. The electric potentials of young persons are higher than those of older persons; thus a lesion in a young person might produce a record having a fairly strong alpha rhythm and a high potential delta activity, whereas an equally damaging lesion in an older person might produce a less persistent alpha rhythm and a somewhat lower potential delta activity. The more rapidly growing tumors tend to produce higher potentials and slower frequencies than do the more slowly growing tumors. Thus, the malignant meningiomas produced a wave pattern similar to that of the gliomas. The final analysis is determined by an evaluation of the record as a whole. A comparison is made of the wave forms from all regions of the head.

This evidence indicates that by means of the electroencephalogram one can ascertain the kind of cerebral pathologic process to a limited degree.

TABLE 3.—*Lesions as Found at Operation or Necropsy Compared with Lesions as Suggested by Nature of Delta Waves Before Operation in 100 Cases of Lesions of the Frontal Lobes*

| | | Estimated Type of Delta Wave in Electroencephalogram | | | | | |
|---|---|---|---|---|---|---|---|
| | | Group 1 | | Group 2 | | Group 3 | |
| Lesion Found to Be | Total No. | No. | Per Cent | No. | Per Cent | No. | Per Cent |
| Meningioma | 26 | 19 | 83 | 6 | 10 | 1 | 6 |
| Glioma | 54* | 1 | 4 | 44† | 76 | 8 | 44 |
| Non-neoplastic | 12 | 2 | 9 | 3 | 5 | 7 | 39 |
| Neoplastic metastasis | 7 | .. | .. | 5 | 9 | 2 | 11 |
| Osteoma | 1 | 1 | 4 | .. | .. | .. | .. |
| Total number | 100 | 23 | 100 | 58 | 100 | 18 | 100 |

* One glioma showing an epileptogenic focus did not fit into any of the groups.

† This group includes 43 records and 1 record which, because of the reduced alpha activity, is included here with group 2.

COMMENT

By coagulating the cortex of monkeys, Dusser de Barenne and McCulloch[7] proved that the electric potentials arise from the neurons of the cerebral cortex. Schwartz and Kerr,[8] as well as Scarff and Rahm,[9] studied the electric potentials obtained from the exposed brain in the presence of tumors. These studies explain why the pathologic character of the lesion can be ascertained to a limited extent by the delta pattern. They showed that in all instances the tumor tissue was inactive and that the effect of the tumor on the surrounding cortical tissue was the basis of the production of potentials of high amplitude and slow frequency. Scarff and Rahm demonstrated that the damage to portions adjacent to benign and encapsulated tumors was small and that there was slight or no retardation of the spontaneous cortical waves. Conversely, malignant and invasive tumors, such as spongioblastomas, were shown to damage the surrounding brain tissue over a much wider region, destroying the normal, spontaneous electric activity. There was a tendency for normal potentials to reappear remote from the tumor mass.

In the cases of meningioma considered in this paper the delta focus was circumscribed and the beta activity, frequently characteristic of the frontal regions, was found to be altered only slightly, if at all. In contrast, in the cases of glioma there was a widespread, slow, high potential type of delta wave with pronounced destruction of the spontaneous electric activity.

The observations of Walter, Griffiths and Nevin[10] substantiated the impression that the generalized delta activity is a result of injury to subcortical centers by invasive tumors. Walter and his associates studied a case of hypothalamic tumor associated with a pathologic disturbance of sleep which produced diffuse, slow, random delta waves even though the cortex and the white matter were normal. This observation may account for the rather pronounced generalized delta activity associated with the spongioblastomas. This activity appears to be secondary to a remote influence occasioned by damage to the deeper centers. In contrast, the benign meningiomas give rise to a more moderate form of diffuse delta activity because of less damage to deep centers.

The work of Bucy and Case[11] tends to confirm the belief that disruption of the occipital alpha rhythm may be caused by interference with the conduction of impulses over the association fibers. Bucy and Case noted that unilateral loss of occipital alpha activity, when associated with homonymous hemianopsia, is the result of destruction of the optic radiations. Here the alpha rhythm is considered a cyclic electric phenomenon circulating in a chain of neurons, one link of which is the optic radiations. Although homonymous defects were not noted generally, other neuron systems in the transcerebral association mechanisms could well account for the disrupted alpha rhythm in the cases considered in this paper.

The aforementioned observations of Walter and his group[10] and those of Bucy and Case also might explain why in 6 of the cases of unilateral spongioblastoma multiforme bilateral frontal delta localizations with loss of spontaneous electric activity were observed. The invasion of the neoplasm damages the transcerebral fibers of the corpus callosum as well as the deeper brain centers. This damage interrupts the intracerebral electric circuits, so that abnormal waves appear in the opposite frontal cortex.

In many of the cases in which choked optic disks were noted, there was moderately high potential, sinusoidal electric activity of 5 to 6 cycles per second. This activity was usually intermittent and frequently was associated with the slower, less regular type of generalized delta activity. We were impressed with the idea that this wave pattern somehow was related to increased intracranial pressure, as manifested clinically by choking of the optic disks. Walter, in further discussing his case of hypothalamic tumor, distinguished the slow, high potential, irregular waves caused by this lesion from the somewhat faster and lower potential waves associated with edema of the brain. Williams[12] attributed the rhythmic, moderately slow electric activity, which was distributed uniformly over the cerebral cortex, to interference with conduction of the fiber tracts as a result of edema of the

7. Dusser de Barenne, J. G., and McCulloch, W. S.: Some Effects of Laminar Thermocoagulation upon the Local Action Potentials of the Cerebral Cortex of the Monkey, Am. J. Physiol. **114**:692-694 (Feb.) 1936.

8. Schwartz, H. G., and Kerr, A. S.: Electrical Activity of the Exposed Human Brain: Description of Technic and Report of Observations, Arch. Neurol. & Psychiat. **43**:547-558 (March) 1940.

9. Scarff, J. E., and Rahm, W. E., Jr.: The Human Electrocorticogram, Tr. Am. Neurol. A. **66**:20-25, 1940.

10. Walter, W. G.; Griffiths, G. M., and Nevin, S.: The Electro-Encephalogram in a Case of Pathological Sleep Due to Hypothalamic Tumour, Brit. M. J. **1**:107-109 (Jan. 21) 1939.

11. Bucy, P. C., and Case, T. J.: An Association Between Homonymous Hemianopsia and Unilateral Absence of the Alpha Waves, Tr. Am. Neurol. A. **66**: 17-20, 1940.

12. Williams, D.: The Abnormal Cortical Potentials Associated with High Intracranial Pressure, Brain **62**: 321-334 (Sept.) 1939.

white matter. This activity seems to be similar to that associated with edema of the brain, as described by Walter and others.[10] The edema depends on an alteration of water balance or ionic concentration in the tissue, that is, a disturbance of the osmotic pressure of the cellular tissue in the white matter of the hemispheres. The cortex is not involved.

Again, in the cases in which choking of the optic disks was present, there was demonstrated a rhythmic electric activity of 5 to 6 cycles per second, as well as slower, irregular, diffusely distributed delta waves. On this basis, the hypothesis might be established that two factors exert an influence on the combined electroencephalographic picture: first, edema of the white matter, producing the rhythmic wave form by partially interfering with the neuronal conduction, and, second, the conduction of impulses over fiber tracts from remote areas, producing slow, irregular, generalized delta activity.

## SUMMARY

In a review of 100 consecutive cases of verified lesions of the frontal lobes of the brain in which electroencephalographic recordings were made, the procedure was found to be valuable in localization of the lesion because of its simplicity and ready applicability. By utilizing the information gained from the electroencephalogram, one may obtain a clue to the pathologic nature of the underlying lesion.

# SCHIZOPHRENIC REACTION SYNDROME IN COURSE OF ACUTE DEMYELINATION OF CENTRAL NERVOUS SYSTEM

## CLINICOPATHOLOGIC REPORT OF A CASE, WITH BRIEF REVIEW OF THE LITERATURE

LEON ROIZIN, M.D.

Associate Research Neuropathologist, New York State Psychiatric Institute and Hospital

NEW YORK

LIEUTENANT (JG) JOHN D. MORIARTY, MC-V(S), U.S.N.R.*

AND

ANDRE A. WEIL, M.D.

Director of Research, New Hampshire State Hospital, Concord, N. H., and Graduate Assistant in Neurology, Massachusetts General Hospital, Boston

CONCORD, N. H.

There is much controversy among various authors concerning the clinical diagnosis of certain schizophrenic syndromes which are associated at times with doubtful neurologic signs and with which definite organic changes in the brain appear. This difference of opinion arises from the fact that some authors explain the mental symptoms on the basis of psychogenic mechanisms while others believe that these symptoms may be the expression of organic changes.[1]

It seems to us that it is of interest and importance that both clinicians and neouropathologists take into consideration the fact that, besides psychogenic mechanisms, various somatogenic factors, acting independently or in combination, may precipitate a schizophrenic syndrome.[2]

* Formerly Assistant Physician at the New Hampshire State Hospital, Concord, N. H.

From the Department of Neuropathology of the New York State Psychiatric Institute and Hospital, New York, and from the New Hampshire State Hospital, Concord, N. H.

1. Alzheimer, A.: Beiträge zur pathologischen Anatomie der Dementia Praecox, Ztschr. f. d. ges. Neurol. u. Psychiat. **7**:621, 1913. Cotton, H. A.: Fatty Degeneration of the Cerebral Cortex in the Psychoses, with Special Reference to Dementia Praecox, J. Exper. Med. **22**:492, 1915. Josephy, H.: Beiträge zur Histopathologie der Dementia Praecox, Ztschr. f. d. ges. Neurol. u. Psychiat. **86**:391, 1923. Fünfgeld, E.: Ueber die pathologische Anatomie der Schizophrenie und ihre Bedeutung für die Abtrenung "atypischer periodisch verlaufender Psychosen," Monatschr. f. Psychiat. u. Neurol. **63**:1, 1927. Buscaino, V. M.: Ricerche istoneuropatologiche, encephalografiche e del liquor in dementi precoci (con un'appendice sulle "zolle di disintegrazione a grappolo"), Riv. di pat. nerv. **34**: 181, 1929. Hechst, B.: Zur Histopathologie der Schizophrenie, Ztschr. f. d. ges. Neurol. u. Psychiat. **134**:163, 1931. Freeman, W.: Lipoid Degeneration Products in the Thalamus and Globus Pallidus in Schizophrenia with a Note on Calcification, A. Research Nerv. & Ment. Dis., Proc. **5**:382, 1928; Deficiency of Catalytic Iron in the Brain in Schizophrenia, Arch. Neurol. & Psychiat. **24**:300 (Aug.) 1930. Ferraro, A.: Histopathological Findings in Two Cases Clinically Diagnosed Dementia Praecox, Am. J. Psychiat. **13**:883, 1934. Elvidge, A. R., and Reed, G. E.: Biopsy Studies of Cerebral Pathologic Changes in Schizophrenia and Manic-Depressive Psychoses, Arch. Neurol. & Psychiat. **40**:227 (Aug.) 1938. Bruetsch, W. L.: Chronic Rheumatic Brain Disease in Schizophrenia, Am. J. Psychiat. **97**:276, 1940; Late Cerebral Sequelae of Rheumatic Fever, in Annual Report of the Central State Hospital, Indianapolis, Ind., 1943. Kirschbaum, W. R., and Heilbrunn, G.: Biopsies of the Brain of Schizophrenic Patients and Experimental Animals, Arch. Neurol. & Psychiat. **51**:155 (Feb.) 1944.

2. (*a*) Bleuler, E.: La schizophrenie, Rev. neurol. **2**:474, 1926; (*b*) Textbook of Psychiatry, New York, The Macmillan Company, 1930. (*c*) Menninger, K. A.: The Schizophrenic Syndrome as a Product of Acute Infectious Disease, A. Research Nerv. & Ment. Dis., Proc. **5**:182, 1928. (*d*) Campbell, M. C.: On the Definition or Delimitation of Schizophrenic Type of Reaction, ibid. **5**:16, 1928. (*e*) Hutchings, R.; Cheney, C. I., and Wright, W. W.: Psychogenic Precipitating Causes of Schizophrenia, ibid. **5**:159, 1928. (*f*) Jelliffe, S. E.: The Schizophrenic Group, J. Nerv. & Ment. Dis. **74**:347 and 543, 1931. (*g*) May, G. V.: The Dementia Praecox–Schizophrenia Problem, Psychiatric Quart. **6**:40, 1932. (*h*) Courtois, A., and Borel, J.: Encéphalopathie de l'enfance, Syndrome de démence précoce, Rev. neurol. **1**:299, 1932. (*i*) Courtois, A.: Certains agents étiologiques des syndromes de démence précoce, Ann. méd.-psychol. (pt. 2) **93**:51, 1935. (*j*) Goldstein, K.: Zur pathologischen Anatomie der Dementia praecox im besonderen der plötzlichen Todesfalle bei derselben, Monatschr. f. Psychiat. u. Neurol. **25**:565, 1909. (*k*) Kronfeld, A. S.: Schizophrenia-like Psychosis in Patients with Organic Brain Disease, Sovet. psikhonevrol. **16**:92, 1940. (*l*) Shapiro, L. B.: Schizophrenic-like Psychosis Following Head Injuries, Elgin State Hosp. Papers **4**:153, 1941. (*m*) Kimball, I.: Schizophrenic and Organic Reaction Type of Psychoses, Kentucky M. J. **41**:346, 1943. (*n*) Polatin, P.; Eisenstein, V. W., and Barrera, S. E.: Organic Psychosis Simulating Dementia Praecox, Psychiatric Quart. **18**:391, 1944.

In support of this view, we shall limit ourselves to presenting and discussing one type of organic cerebral change which may precipitate clinical manifestations of the schizophrenic type.

## REPORT OF CASE

B. G., a 34 year old married white woman, a factory worker, entered the New Hampshire State Hospital on Jan. 9, 1942, on a regular commitment. Three weeks previously the patient had begun to complain of "trouble with her throat." She spoke in a whisper and stated that she was unable to talk out loud. Examination by an otolaryngologist revealed nothing abnormal. Four days later the patient appeared unable to speak at all and could not, or would not, eat or swallow. When taken to a general hospital, she seemed to recognize people about her and wrote brief notes to communicate with them. However, she soon became restless, slept poorly and had to be fed with a tube. Examination by a neuropsychiatrist at this time revealed that she was "listless" and at times "exhibitionistic, uncovering and exposing herself." This specialist indicated, also, that the patient was "quite aware of her environment." Neurologic examination at that time was reported to reveal an essentially normal condition except for active tendon reflexes and absence of plantar, abdominal and corneal reflexes. No signs of bulbar paralysis were elicited; the condition of the spinal fluid was within normal limits. The patient was committed with a diagnosis of "major hysteria (?), catatonia."

*Personal History.*—Birth and early development were normal. The patient graduated from grammar school at the usual age. Shortly afterward she went to work in a shoe factory and continued at that occupation until her present illness. She was married at the age of 21 to her present husband. The only child of the union died at the age of 2 years, of pneumonia. The patient showed a normal amount of grief at her child's death. Aside from mild neurotic traits, she showed no psychopathologic manifestations until the onset of the present illness. The medical history was noncontributory except that during the past three years the patient had been bothered with occasionally "losing her voice." This disturbance would last only a day or so and would then disappear as rapidly as it had come.

*Family History.*—There was no family history of nervous or mental disorder except that an older brother had been hospitalized three years previously for a condition diagnosed as dementia paralytica. Despite malarial fever treatment, he died of this disorder two months after admission. Autopsy was not performed.

*Physical Examination.*—On admission the patient was asthenic, rather poorly nourished and somewhat dehydrated. The blood pressure was 120 systolic and 82 diastolic, the temperature 99.6 F., the pulse rate 104 and the respiration rate 22.

*Neurologic Examination* (in consultation).—The report follows: "The patient understood the meaning of questions and was able to answer simple questions by sign language. She was slightly resistive when asked to open her mouth or to smile. The disks were clearly outlined. The blood vessels were of normal caliber. The motor system was normal. Vibration sense was reduced on the left, but the results were hard to evaluate.

"Reflexes: The biceps and triceps reflexes were 1 to 2 plus; the knee jerk was 2 to 3 plus, and the ankle jerk, 1 plus; an ankle clonus was elicited on the left. Abdominal reflexes were not elicited. No abnormal reflexes were obtained.

"Impression: No evidence of local damage to patient's nervous system was found. The aphasia was not typical of organic disease of the brain and probably was on a schizoid or hysterical basis."

*Laboratory Data.*—The Hinton reaction of the blood was negative; the blood count was normal throughout. Urinalysis gave normal results except for a positive reaction for acetone. Examination of the spinal fluid had been previously reported as showing nothing abnormal.

*Mental Status and Course in the Hospital.*—The patient was cared for in the admission ward during her entire stay in the hospital. She remained in what appeared to be a catatonic stupor. Thus, most of the time she would lie in bed staring with a wooden expression at the ceiling and not responding to ordinary stimuli. Occasionally she showed impulsive behavior. Thus, she would throw off her bedclothes in an exhibitionistic way. A few times she tore off the clothing for no apparent reason and with no regard for who might observe her. For the most part it was difficult or impossible to obtain her attention or to make contact with her. However, once in a while, when her attention was obtained, she would gesture toward her throat and would stroke it with both hands, as though trying to indicate that the site of the trouble was there. During the first part of her stay in the hospital psychomotor activity was increased for short periods. During these episodes the patient moved restlessly about the ward, annoying the other patients, although she took little notice of them. Her facial expression was bewildered and perplexed. After a few days she refused to get out of bed and refused food. When an attempt was made to urge her to take nourishment, she became resistive. The most she would ever do was to swallow a few sips of milk. Thus it became necessary to feed her by tube daily.

At no time during her stay in the hospital did the patient speak audibly, but during the first week she would occasionally try to form words with her lips. Emotionally she appeared somewhat depressed; her manner was preoccupied and withdrawn. On one or two occasions she showed flashes of apprehension. These reactions were apparently motivated from within.

Because of her muteness, no idea of her mental content could be obtained. On the basis of observations, she seemed to be reacting to auditory hallucinations, in that she at times showed an attitude which might be described as listening. Although it was impossible to evaluate the state of her sensorium precisely, it appeared evident that she recognized persons about her, at least during the first week of her stay in the hospital, and that she appreciated the fact that she was in a hospital.

On the assumption that hysterical elements might be present, hypnotism was tried first in the treatment of her disorder, but she remained entirely resistant to this form of therapy. Likewise, her condition appeared quite unaffected when 15 grains (0.975 Gm.) of sodium amytal was given intravenously. After a week's study, the patient was given a course of three metrazol convulsion treatments. Despite this, her clinical condition remained basically unchanged, and the treatments accordingly were discontinued. Tube feedings had to be maintained. The patient tended to gag and cough rather excessively with each feeding. Two weeks after admission a moderate fever with a rectal temperature of 102.5 F. developed, and signs of patchy consolidations appeared in the lungs. She failed rapidly and died on January 24. The clinical

cause of death was given as bronchopneumonia due to aspiration, with inanition as a contributing cause.

*Summary.*—The patient was a 34 year old white woman with no past history of mental or nervous illness and an apparently negative family history in this respect. The illness in question was noteworthy for its extreme suddenness of onset, the lack of response to shock treatment and the rapidly fatal course.

In view of the increased psychomotor activity (in the beginning of the illness), followed by negativism, some stereotopy, resistiveness, mutism, refusal to eat and a rapid downhill trend, most staff members of the New Hampshire State Hospital felt that the clinical course in this case resembled schizophrenia of the catatonic type.

However, at the very onset of the clinical symptoms there was a question of major hysteria, as suggested by mutism, apparent inability and refusal to swallow and apparent aphonia. In favor of such an evaluation of the symptoms was the absence of any motor defects of the tongue, lips or larynx and absence of outbursts of laughing and crying, so often observed with the supranuclear type of palsy.

Even though left ankle clonus and somewhat increased patellar reflexes were present, in addition to the absence of corneal and abdominal reflexes, two neurologists who were called in consultation stated the belief that the clinical picture was not to be considered that of a neurologic disorder. On such grounds and because the mental symptoms dominated the clinical picture, the diagnosis of schizophrenic syndrome, catatonic type, was retained throughout the life of the patient.

*Autopsy.*[3]—The gross pathologic changes consisted of (1) multiple, small abscesses of both lungs; (2) several areas of a purulent inflammatory process over the pleura of the lower lobes of both lungs, and (3) apparently normal meninges and brain. However, in one section of the brain a number of small, bilateral, roughly symmetric areas, almost serpiginous in outline, were found in the subcortical regions of the frontal and parietal lobes (fig. 1). The consistency of such areas was peculiarly gelatinous. A few similar areas were noticed likewise in the medulla near the pons. Otherwise, the brain appeared grossly normal.

Microscopic examination confirmed the presence of small abscesses in the lungs and an acute inflammatory exudate over the pleura. Smears from the pulmonary abscesses showed various types of both rod and coccus forms of bacteria.

*Microscopic Examination of Central Nervous System.*—Blocks from the prefrontal, frontal, parietal and temporal cortex, the basal ganglia and the medulla were studied after fixation in alcohol and diluted solution of formaldehyde U. S. P.. The usual neuropathologic technics were employed, as well as some histochemical reactions for fatlike substances and myelin products of disintegration.

With stains for myelin sheaths, considerable demyelination involving in variable degree most parts of the white matter of the frontal and parietal lobes bilaterally and symmetrically was observed. Some of the demyelinated areas appeared sharply outlined, whereas others less well demarcated assumed the aspects of the "transitional type" of demyelination. Generally, these demyelinated areas were limited to the subcortical white matter, but occasionally the U fibers and the deep cortical layers were involved. In certain instances the irregular appearance and distribution of the demyelination reproduced roughly the aspect of Marburg's "geographic map-like" variety of demyelination.

The intensity of the demyelination was irregular (fig. 2 *A*). In some areas there were only rarefaction, swelling and slight degeneration of the myelin sheaths. In others the demyelination was almost complete, and only here and there remnants or debris of disintegrated myelin sheaths were noticeable. In others, finally, various stages of transitional alterations were encountered

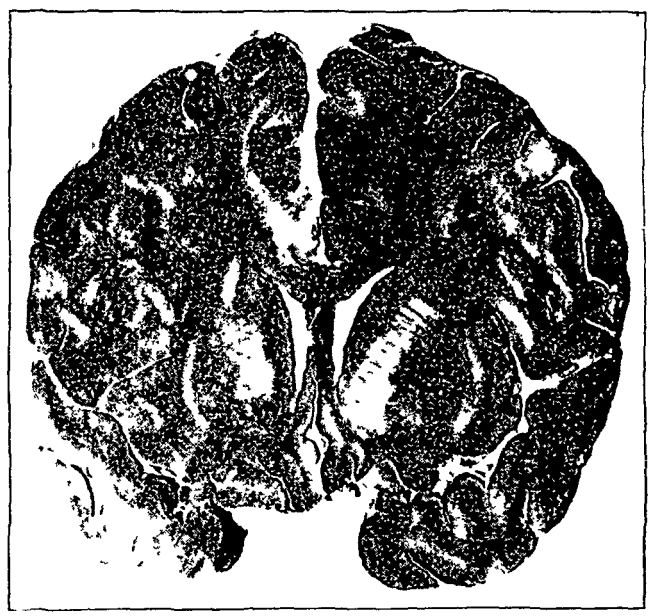


Fig. 1.—Coronal section of the fixed brain through the basal ganglia, revealing the presence of subcortical, bilateral and roughly symmetric areas of softening, of irregular outline; approximately one-half natural size.

(fig. 2 *B* and *C*). In a few areas bands of less intense damage to the myelin alternated with bands of almost complete destruction of myelin, recalling Baló's concentric type of demyelination. Such areas were more distinct when the lipid material was dissolved (fig. 2 *C*).

In the medulla oblongata two small areas of demyelination were present. They were not limited by any anatomic topography.

Some of the demyelinated areas were localized around or near blood vessels (veins or arteries), but in many instances, particularly in the regions of alternating demyelination, no relation to the vascular pattern could be found.

Combined methods for nerve fibers and myelin sheaths revealed that axis-cylinders appeared more resistant than the myelin sheaths. Where the myelinolysis was more severe, scarcely any nerve fibers were left, but only fragments and debris surrounded by large macrophages containing granular material formed by disintegration of myelin; where the demyelination was less intense, more

3. Autopsy was performed by the late Dr. David Dial, of the New Hampshire State Hospital.

axis-cylinders were present, and closer to the borders of the lesions an increasing number of nerve fibers were present and preserved.

Various histochemical methods revealed that the staining and histochemical properties of the fatlike substances and the products of myelin disintegration varied not only from one area to another but at times in the same area. In the areas in which a large amount of fat was present, the substance assumed the form of condensed material free in the tissue or accumulated in compound granular corpuscles (fig. 3 *A*). The perivascular spaces, as well as the adventitial sheaths of the blood vessels, were also laden with many scavenger cells filled with fat material.

However, the so-called argyrophil granules were seen mostly intracellularly in elements having the appearance of large, granulated macrophages (fig. 3 *B*). In the areas where the fatlike substance and products of myelin disintegration were present in less quantity, the material occurred more frequently intracellularly and surrounding the perivascular spaces of some blood vessels. In addition, in some of the involved areas, particularly in the medulla, metachromatically stained bodies were also observed.

We should like to mention only that this variety of histochemical reactions of the fatlike substances and products of degeneration is, in our opinion, related to difference in stage of myelin disintegration.


Fig. 2.—*A*, *B* and *C*, multiple, irregular and transitional type of demyelination, as described in the text; Roizin's combined method for myelin sheaths and lipid products of disintegration; low power magnification.

The distribution and intensity of the macroglial reaction were heteromorphic in character and almost inversely proportional to the process of demyelination. But this was not always the case, for it was also observed that in certain areas of severe destruction of myelin and in areas where the process appeared to be of more recent character the glial proliferation was lacking or was not proportionately so intense as would be expected.

Several cytologic methods revealed in the demyelinated areas various degrees of perivascular infiltration The amount and the character of the cellular elements surrounding the blood vessels varied from area to area: At times the perivascular cuffings consisted of lymphocytes; at others, of gitter cells, and at still others, of a mixture of gitter cells, lymphocytes, large mononuclear cells and plasma cells (fig. 4 *A*). Occasionally, granulomatous formations, composed mostly of lymphocytes and large mononuclear cells, were also observed (fig. 4 *B*). In addition, mixed with the perivascular elements or free in the interstitial tissue, large globoid cells with three or four nuclei were seen scattered here and there (fig. 4 *C* and *D*).

At times small hemorrhages surrounding blood vessels were also encountered (fig. 5 *A*); at others red blood cells were mixed with the perivascular inflammatory elements (fig. 5 *B*). Although the inflammatory cuffings had generally a perivascular distribution, on several occasions the walls of the blood vessels were infiltrated.

In certain instances, the walls of the blood vessels disclosed fibrous thickening of the adventitia or media or hyaline degeneration. Many of the endothelial cells of the infiltrated vessels had swollen nuclei.

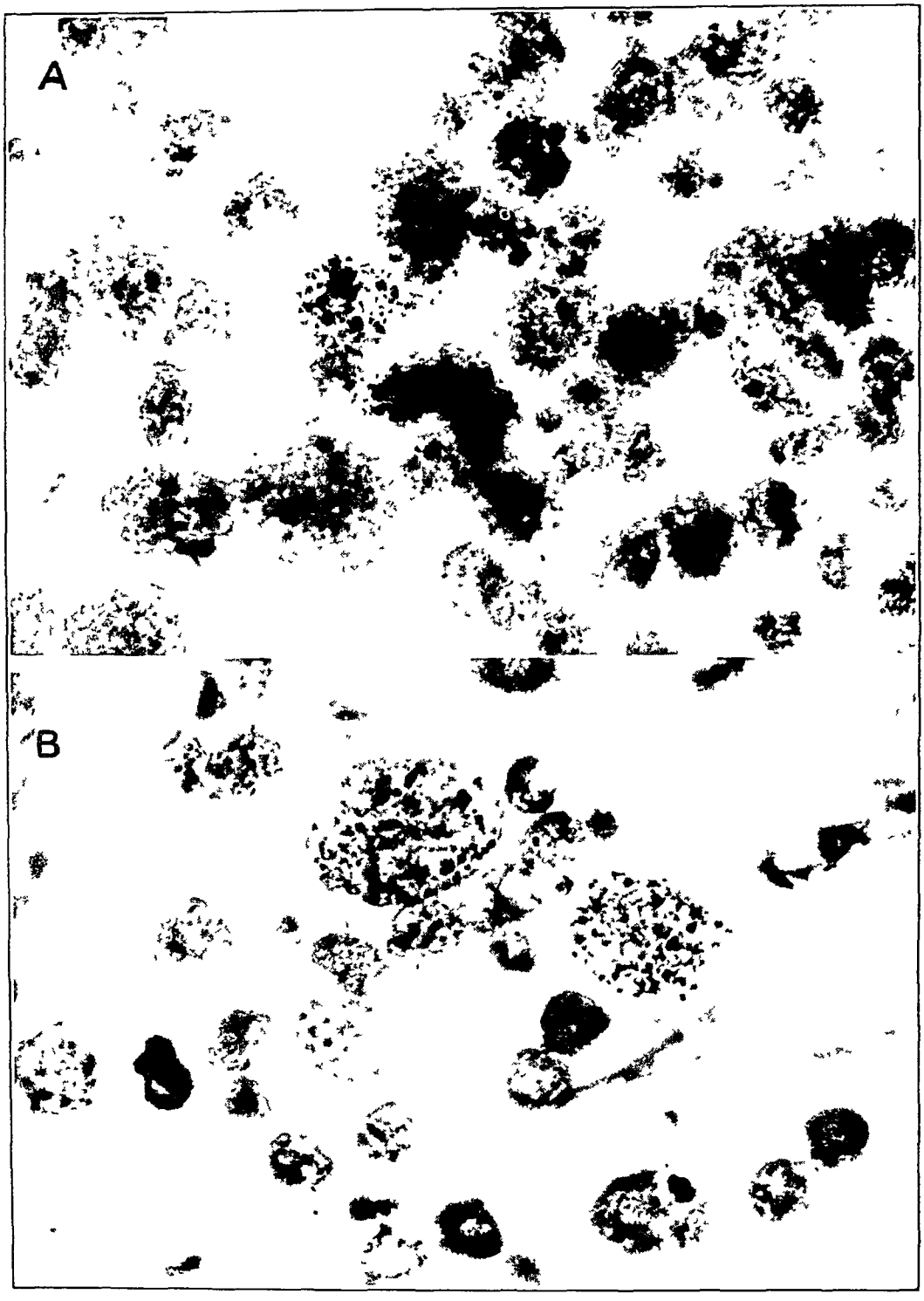



Fig 3.—*A*, compound granular corpuscles, containing various types of lipid products of disintegration; Roizin's combined method for myelin sheaths and lipid products of disintegration. *B*, large phagocytic elements, containing argentophil granular material; ammoniacal silver method; high power magnification.

With the common methods no definite thrombosis was observed.

The cytologic methods did not reveal any appreciable cytoarchitectonic alteration of the cortex, although here and there the presence of individual cells or of groups of cells undergoing tigrolysis, chromatolysis and neuronophagia was noticed. These cellular changes were more frequently observed in the third and fifth layers of the prefrontal, frontal and temporal cortical regions. Occasionally, in the same regions, more severe neuronal changes, as well as small acellular areas, were found. In the middle and deeper cortical layers, as well as in the subcortical zone, numerous oligodendrocytes in the stage of acute swelling were also detected.

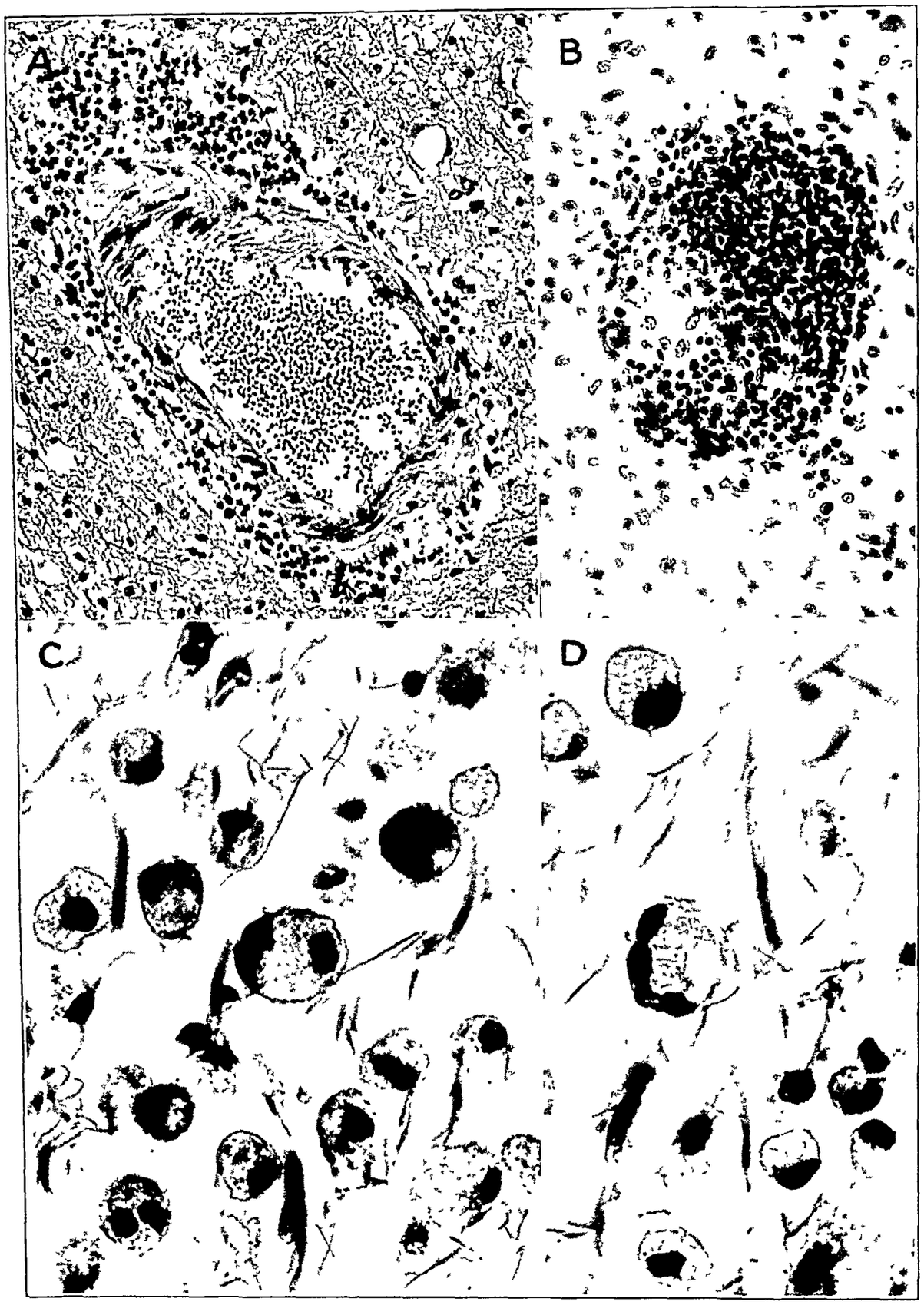



Fig. 4.—*A*, perivascular infiltration, consisting of lymphocytes, gitter cells, large mononuclear cells and some plasma cells; hematoxylin and eosin stain. *B*, perivascular granulomatous formation, composed mostly of lymphocytes and some large mononuclear elements; Nissl stain, medium power magnification. *C* and *D*, globoid cells with two, three or four nuclei; hematoxylin and eosin stain; high power magnification.

From the point of view of histologic diagnosis, in view of the type, character, distribution of the demyelinating process and duration of the disease, this condition may be considered as (1) disseminated en-

cephalomyelitis of unknown nature, or (2) acute multiple sclerosis of Marburg's and Baló's variety. We prefer to use a simple and more comprehensive term, that of a primary demyelinating disease of the central nervous system, of the acute and sporadic type, according to Ferraro's [4] classification.

A great variety of mental symptoms in the course of multiple patchy and diffuse demyelination of the central nervous system have been described by several authors,[5] but in 1 case in particular, that of Holt and Tedeschi,[6] a clinicopathologic syndrome closely resembling ours was presented. We shall recapitulate and discuss this case.

J. E., a white man aged 55, had no history of nervous or mental disease in the family. The past personal history showed nothing of importance except that the patient entered a state hospital for mental disease in 1924. There a diagnosis of dementia precox, catatonic type, was made. Five months later he was discharged as completely recovered, and he showed no abnormal mental symptoms for the next eighteen years, until the onset of the fatal illness, with restlessness and insomnia. He said that people were talking about him, expressed fears of death and spoke of imaginary weddings and funerals. Three days later he was admitted to a state psychiatric hospital. On the first day there he was found lying flat on his back; he did not move or answer questions and showed pronounced flexibilitas cerea. This state was suddenly interrupted by a period of excitement, agitation and destructive and assaultive tendencies. Administration of sedatives had no effect on the excitement. The physical condition of the patient declined rapidly; he became incontinent and untidy. During the night of the seventh day of his illness, the temperature rose to 104 F., and he became cyanotic and dyspneic. Neurologic examination at this stage of the illness as well as one made four days earlier, failed to reveal anything of significance; the blood pressure was 162 systolic and 90 diastolic; examination of the blood and all other laboratory tests gave results within normal limits. Death occurred on the morning of the eighth day of illness.

Autopsy did not reveal anything significant in the chest or the abdominal viscera. The brain was shrunken; the vessels at the base of the brain had thin walls and did not show appreciable arteriosclerotic changes. Histologic studies disclosed features "typical of a primary demyelinating process, characterized by . . . sharp demarcation and limitation of the lesions to the white substance of the brain, . . . [with] relative integrity of the overlying cortex down to and including the arcuate bundles."

## COMMENT

That in the course of schizophrenia neurologic symptoms may be detected is a well established occurrence, if one wishes only to refer to the studies of Muhlig.[7] In 65 of 500 cases of schizophrenia, the author found neurologic signs, such as nystagmus, anisocoria, tremors, poor coordination, occasional dysarthria, facial asymmetry, absence of corneal and pharyngeal reflexes and, in 1 case, nystagmus and a unilateral Oppenheim sign. Claude and associates,[8] in their study of the motor syndrome of catatonic dementia precox, reported also the occasional presence of a Babinski sign. They feel that such a sign is not the expression of a systemic structural pathologic process but the indication of a functional dynamic disturbance.

When such symptoms occur in the course of an acute mental disorder leading to death in a short time, one can see the difficulty in evaluating their exact meaning.

In our case the dominant picture was undoubtedly a mental disturbance, and the presence of certain neurologic signs could be interpreted in either of two ways, i. e., as an expression of an organic change in the brain or as an expression of a functional disturbance. If our patient had died without benefit of an autopsy, all the neurologic signs described and initially thought to be of functional nature would have been recorded finally as such. The observations at necropsy and the histologic studies of the case made it necessary, however, to revise the evaluation of such symptoms, and any doubt concerning the original interpretation of the neurologic symptoms is justified.

4. Ferraro, A.: Primary Demyelinating Processes of the Central Nervous System (An Attempt at Unification and Classification), Arch. Neurol. & Psychiat. **37**:1100 (May) 1937.

5. (*a*) Claude, H.; Lhermitte, J., and Baruk, H.: Pathologie de la pré-sénilité. Syndrome catatonique avec négativisme unilateral; aphasie, trouble pseudo-bulbaires. perturbations de la nutrition générale par encéphalose diffuse, Encéphale **27**:175, 1932. (*b*) Guttmann, E.: Die diffuse Sklerose, Zentralbl. f. d. ges. Neurol. u. Psychiat. **41**:1, 1925. (*c*) Weimann, W.: Zur Kenntnis der sogenannten "diffuse Hirnsklerose," Ztschr. f. d. ges. Neurol. u. Psychiat. **104**:411, 1926. (*d*) Löwenberg, K., and Fulstow, M.: Atypical Diffuse Sclerosis, Arch. Neurol. & Psychiat. **27**:389 (Feb.) 1932. Courtois and Borel.[2h] (*e*) Bouman, L.: Diffuse Sclerosis (Encephaliltis Periaxialis Diffusa), Bristol, John Wright & Sons, Ltd., 1934 (cases 3 and 4). (*f*) Wertham, F.: Small Foci of Demyelinization in the Cortex and Spinal Cord in Diffuse Sclerosis, Arch. Neurol. & Psychiat. **27**:1380 (June) 1932 (case 2). (*g*) Gans, cited by Bouman.[4c] (*h*) Ferraro, A.: Pathological Changes in the Brain of a Case Clinically Diagnosed Dementia Praecox, J. Neuropath. & Exper. Neurol. **2**:84, 1943. (*i*) Cardona, F.: Istologia della malattia di Schilder familiare, Riv. di pat. nerv. **54**:1, 1939 (case 1). (*j*) Roizin, L.; Helfand, M., and Moore, J.: Disseminated, Diffuse and Transitional Demyelinations of the Central Nervous System, J. Nerv. & Ment. Dis. (case 3), to be published.

6. Holt, E. K., and Tedeschi, C.: Cerebral Patchy Demyelination, J. Neuropath. & Exper. Neurol. **2**:306, 1943.

7. Muhlig, W. A.: Schizophrenia—Neurologic Signs, J. Michigan M. Soc. **39**:116, 1940.

8. Claude, H.; Baruk, H., and Thévenard, A.: Le syndrome moteur de la démence précoce catatonique, Encéphale **22**:741, 1927.

The fundamental organic cerebral process in our case was one of acute demyelination. Some authors might define the pathologic process as Schilder's disease, or encephalitis periaxialis diffusa. We prefer to call it an acute demyelinating condition, following Ferraro's [4] concept of grouping together all the demyelinating diseases, in an attempt to eliminate confusion and a variable nomenclature for the same fundamental clinicopathologic process.

What we wish to emphasize with the description of our case is the fact that organic processes of the brain may precipitate a syndrome which from the clinical standpoint is predominantly a mental one and that such a syndrome may possess all or most of the features of what clinically we consider an acute schizophrenic syndrome.

It is not our intention to build up an organic concept of schizophrenia. We wish only to focus attention on the possibility that acute mental syndromes which have all the earmarks of a so-called functional psychosis may ultimately prove to be a collection of symptoms precipitated by a definite organic disease of the brain. The need for emphasis on such an occurrence is quite evident when one considers the possibility that some of these acute schizophrenic syndromes may lead to death without the benefit of an autopsy control.

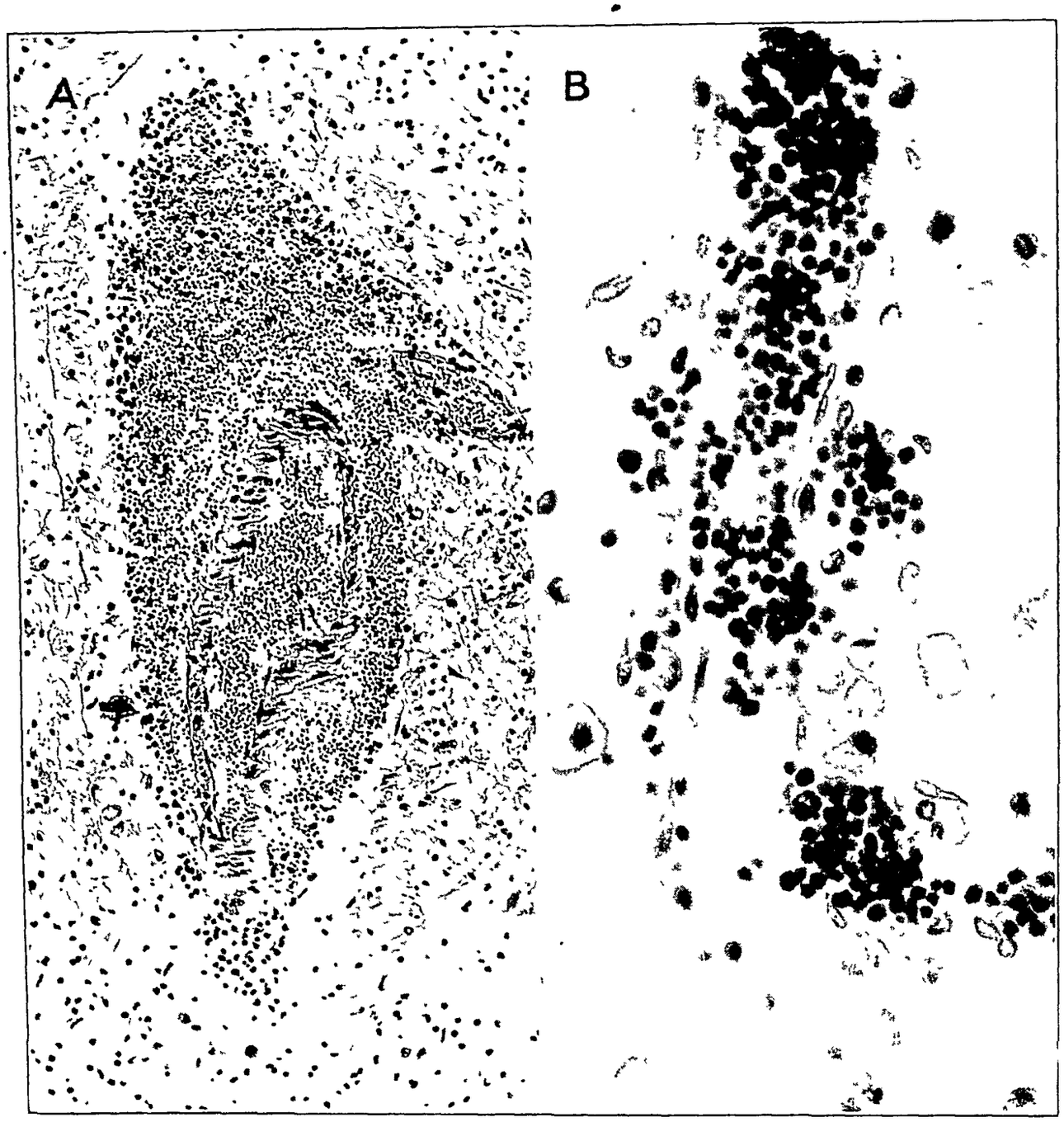



Fig. 5.—*A*, perivascular hemorrhages surrounded at its periphery with perivascular inflammatory cells; hematoxylin and eosin stain, medium power magnification. *B*, diapedesis, red blood cells in an area of demyelination; hematoxylin and eosin stain, high power magnification.

The case which we have described had definite pathologic clinical features in common with the case of an acute schizophrenic catatonic syndrome described by Holt and Tedeschi.[6] These common features are: (1) increased psychomotor activity, stereotopy, impulsiveness, bewilderment, nega-

tivism and possible hallucinations; (2) short duration of the disease and rather sudden death; (3) fleeting neurologic signs, the value of which was debatable during the patient's life, and (4) presence in the central nervous system of a process of acute demyelination.

In our case, as well as in the case of Holt and Tedeschi,[6] there seems to be no question as to the close relationship between the clinical symptoms and the pathologic changes, as evidenced by the relatively short duration of the illness and the rather recent type of the morphologic process.

However, the relationship between cerebral organic changes and the clinical syndrome of schizophrenia in the cases of so-called chronic disease becomes a more complicated problem. In these cases evaluation of such a relationship is extremely important. In the presence of pathologic changes in cases of chronic schizophrenia one must consider the following possibilities, as emphasized by Ferraro:[9] (*a*) The changes may be the expression of organic complications in the course of schizophrenia; (*b*) the changes may be the expression of a primary organic disease; (*c*) the changes may be the expression of the composite picture, in which soma and psyche integrate each other.

The acceptance of the first or the second possibility may be confusing or misleading unless the third possibility is first evaluated and accepted or discarded. This third interpretation stems out of the concept that schizophrenia must be viewed from the standpoint of psychosomatic integration. The organic cerebral change could, therefore be considered neither as the cause nor the complication of schizophrenia but as the result of interplay of soma and psyche in the determination of the structural pathologic process.

In our case, however, this third possibility does not apply, and the case falls into the second group, in which the clinical symptoms are precipitated or activated by a primary organic disease (demyelination).

In this connection, the case of Holt and Tedeschi[6] is instructive, since their patient had an acute schizophrenic episode of the catatonic type as far back as 1924, recovering from it five months later. We do not know what precipitating factors at that time determined this clinical manifestation. The occurrence of such a schizophrenic episode indicates that in their case there could have existed a constitutional predisposition to react along a schizophrenic pattern. This pattern of reaction, which in 1924 might have been precipitated by psychogenic stimuli, was produced eighteen years later by an organic disease of the brain. Such considerations emphasize the fact that in the background of our case, as well as of the case of Holt and Tedeschi, there must have been a potential tendency to react along schizophrenic lines and that irrespective of the precipitating factor, whether psychogenic or organic, the schizophrenic pattern presented itself as the dominant clinical manifestation.

It is not the place here to discuss what determines the constitution to react along certain patterns. Such a constitution in schizophrenia might be the expression of heredity, as well as of structural pattern in terms of biochemical lability or of morphology, in which the vascular[10] and vegetative systems[11] or the endocrine and general metabolic processes[12] may play a role. We feel, however, that constitutional factors are not sufficient in themselves to bring about a mental syndrome but that constitutional predisposition must be activated by precipitating factors of either psychogenic or organic nature. In our case an organic precipitating factor brought about the development of a symptom complex which clinically was diagnosed as a schizophrenic syndrome.

SUMMARY

A clinicopathologic study was made of a 34 year old woman who died after a brief, acute psychosis, presenting the clinical features of a

9. Ferraro, A.: Recent Advances and Progressive Trend of Neuropathology in Psychiatry, Psychiatric Quart., to be published.

10. Lewis, N. D. C.: The Constitutional Factors in Dementia Praecox, Nervous and Mental Disease Monograph 35, New York, Nervous and Mental Disease Publishing Company, 1923; Research in Dementia Praecox, New York, National Committee for Mental Hygiene, 1936.

11. Eppinger, H., and Hess, L.: Vagotonia (A Clinical Study in Vegetative Neurology), New York, Nervous and Mental Disease Publishing Company, 1917. Kempf, E. J.: Psychopathology, St. Louis, C. V. Mosby Company, 1920. Laignel-Lavastine, M.: The Concentric Method in the Diagnosis of Psychoneurotics, New York, Harcourt Brace and Company, Inc., 1931.

12. Mott, F. W.: Etat des organes sexuels dans la démence précoce (en rapport avec l'origine genitale de cette affection), Encéphale **18**:73, 1923. Bowman, K. M.: Endocrine and Biochemical Studies in Schizophrenia, A. Research Nerv. & Ment. Dis., Proc. **5**:262, 1928; Endocrine and Biochemical Studies in Schizophrenia, J. Nerv. & Ment. Dis. **65**:465, 1927. Whitehorn, J. C.: Effects of Glucose upon Blood Phosphates in Schizophrenia, A. Research Nerv. & Ment. Dis., Proc. **5**:257, 1928; Review of Psychiatric Progress 1942; Endocrinology, Biochemistry and Neuropathology, Am. J. Psychiat. **99**:595, 1943. Hoskins, R. G., and Sleeper, F. H.: Organic Functions in Schizophrenia, Arch. Neurol. & Psychiat. **30**:123 (July) 1933. Looney, J. M., and Freeman, H.: Volume of Blood in Normal Subjects and in Patients with Schizophrenia, ibid. **34**: 956 (Nov.) 1935. Gjessing, R.: Beiträge zur Kenntnis der Pathophysiologie periodisch katatoner Zustände: Versuch einer Ausgleichung der Funktionsstörungen, Arch. f. Psychiat. **109**:525, 1939. Ferraro.[9]

schizophrenic reaction syndrome (catatonic type). Neuropathologic studies revealed a symmetric acute demyelinating process of the central nervous system, of unknown nature.

The relationship between the clinical symptoms and the pathologic changes is emphasized not to create an organic concept of schizophrenia but merely to illustrate that a demyelinating process acting as a somatogenic factor may precipitate, in certain cases, an acute mental syndrome, which may or may not be associated with fleeting neurologic symptoms, the evaluation of which is at times difficult. The clinical characteristics of the acute mental episode may at times assume the features of a typical acute schizophrenic syndrome, and such a diagnosis might be retained throughout the life of the patient.

722 West One Hundred and Sixty-Eighth Street.

# A VISUAL RETENTION TEST FOR CLINICAL USE

LIEUTENANT COMMANDER ARTHUR L. BENTON, H(S), U.S.N.R.

The visual retention test to be described here was developed as a practical means of fulfilling what I have long felt to be a need in the usual clinical examination of patients, namely, a short test to supplement the auditory-vocal digit span test in the investigation of immediate memory.

The auditory-vocal digit span test, devised in 1887 by Jacobs,[1] has become a stable feature of most clinical examination schemes. It measures retention or immediate memory, which is justifiably considered to be a significant aspect of mental capacity and one which is especially important clinically because of its close relationship to mental impairment. The test has obvious technical advantages, such as brevity of administration, lack of need for test materials and the objective character of the patient's performance.

Nevertheless, while it is a useful single test, both clinical experience and experimental observations indicate that it cannot be considered to be in itself an adequate measure of retentive capacity and that to make a global judgment concerning a patient's retentive capacity on the basis of this test alone, as is so often done, is quite unwarranted. Clinical experience shows that a poor performance on the auditory-vocal digit span test is by no means necessarily indicative of defective retentive capacity. It is well known that emotional tension can significantly impair performance on the test. Indeed, continued experience suggests that it is a test which is unusually sensitive to emotional influences. Consequently, a poor performance in a tense patient does not permit unequivocal interpretation. The poor performance might be due to emotional disturbance; yet one has no evidence that this is necessarily the case. The whole performance, therefore, must be discounted as neither indicating nor ruling out impairment in retention. Since the possibility of emotional disturbance should be considered in all instances of defective performance on the test, even when emotional tension may not be obvious, defective performance is always open to question unless it is supported by defective performances on other retention tests. In addition, one observes that a certain proportion of normal persons who exhibit no defects in the performance of other mental tasks or retention tests do poorly on this test. The reasons for these defective performances on the part of some normal subjects are not well established and can be counted only as the expression of the range of "individual differences" to be found in the measurement of any trait. Finally, the inadequacy of a single retention test like the auditory-vocal digit span is quite evident when one considers the frequently specific nature of neuropathologic disabilities. A patient's "auditory memory" may be intact at the same time that his "visual memory" is defective. His performance on a retention task involving speech as the motor response may be adequate, while the same task involving graphic activity as the motor response evokes a defective performance.

In this respect, four characteristics of the auditory-vocal digit span test which define its specific nature and which allow for "normal" variations in efficiency in respect to each characteristic should be mentioned: (1) The sensory component is auditory; (2) the motor component is vocal; (3) the material to be retained (numbers) is of a symbolic nature; (4) the test is an "interpersonal" task, involving a constant vocal exchange between patient and examiner.

Experimental psychologic investigation has indicated that when a number of retention tests are given to a group of subjects, the intercorrelations of the scores are not high enough to warrant the substitution of one test for another. Statistical analysis of test results [2] have yielded evidence for the existence of an "immediate memory factor," but as yet an adequate single test for the valid assessment of this "immediate memory factor" has not been devised. The practical implications of the experimental work on the problem are clear. In the present state of knowledge of memory functions and of mastery of

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth in this article are those of the writer and are not to be construed as reflecting the policies of the Navy Department.

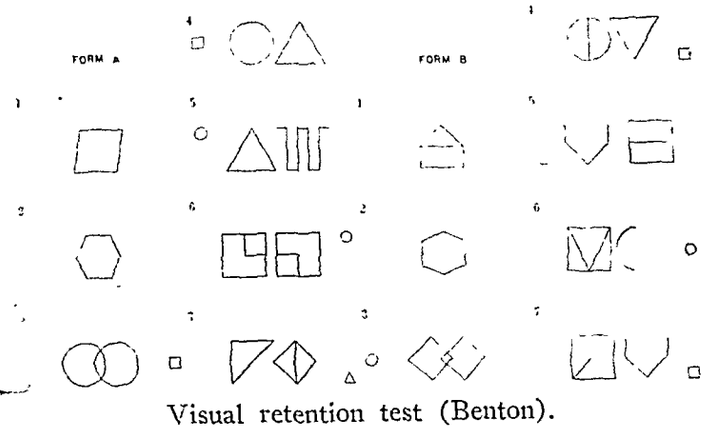
1. Jacobs, J.: Experiments on "Prehension," Mind **12**:75-79, 1887.

2. Thurstone, L. L.: Primary Mental Abilities, Psychometric Monograph, no. 1, Chicago, University of Chicago Press, 1938.

the technic of their measurement, one cannot depend on one test alone to give a valid index of a patient's retentive capacity.

The retention test which I have devised is a "memory for designs" test, the aim of which is to supplement the auditory-vocal digit span test as a measure of retention. In its construction certain conditions were kept in mind:

1. The test should be brief, so that it can be conveniently employed in a test battery of reasonable length. This condition is considered to have been fulfilled, since the total time required for administration is four minutes.



Visual retention test (Benton).

2. The test should involve sensorimotor components which are different from the auditory-vocal digit span test. This it does in that it utilizes vision as the sensory component and drawing as the motor component.

3. The material to be retained should be of a nonsymbolic nature. This aim is accomplished by utilizing abstract designs rather than numbers, letters, words or pictures.

4. The test should be a less "interpersonal" task than the auditory-vocal digit span test. This condition is fulfilled in that there is no necessity for conversation between patient and examiner after the initial instructions have been given. The patient does not "talk to" the examiner in giving his response but works alone, thereby making the task more impersonal than the digit span test.

5. The test should be of such a degree of difficulty that normal persons rarely do poorly on it, thereby enhancing the diagnostic value of defective performance on the test. The normative data to be presented here indicate that this condition has been fairly well fulfilled.

6. Equivalent forms of the test should be available, so that a patient may be examined with a minimum of practice effect.

## DESCRIPTION OF THE TEST

The visual retention test (figure) consists of seven cards, 5 inches by 8 inches (12.7 by 20.3 cm.), on which one or more designs have been drawn in india ink. The cards are roughly graded in difficulty, the easier ones being presented first. The larger, central, figures have a maximum height and width of 2 inches (5 cm.). The smaller, peripheral, figures have a maximum height and width of 0.5 inch (1.3 cm.). Two sets (forms *A* and *B*) of seven cards each have been constructed.

*Administration.*—The patient is given blank sheets of paper, preferably 5 inches by 8 inches, and a pencil. He is told that he will be shown a design for ten seconds and that when it is removed he is to draw the design. A separate sheet of paper is used for each drawing. Each card is presented without comment. The patient's performance may be praised.

*Scoring.*—The scoring standards have been made extremely lenient, since one is interested not in the patient's drawing ability but in his capacity to retain momentarily a visual impression. Any reproduction which the examiner can consider an essentially correct reproduction, in spite of minor distortions, is counted as a success. A manual of directions, including specific scoring samples, has been written in connection with the test. My experience has been that with the aid of these scoring samples practically perfect agreement in scoring between different raters is achieved. The scoring of a single reproduction is on an "all or none" basis, being graded as adequate or inadequate. Since there are seven cards, scores may range from 0 to 7.

## NORMATIVE DATA

The accompanying table shows the distribution of scores for the group of 160 subjects on whom the test was standardized. The subjects were, with a few exceptions, patients at a Naval hospital. They were almost all men, there being only 5 women in the group. The ages ranged from 17 to 51 years, the median age being 22 years. Some notion of the character of the group may be gained from the following diagnostic classification:

*Distribution of Scores of One Hundred and Sixty Subjects on the Visual Retention Test*

| Group | No. of Subjects | Form | Score 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Mean | Median |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Superior Intelligence | 10 | A | .. | .. | .. | .. | .. | 1 | 6 | 3 | 6.2 | 6 |
| | 14 | B | .. | .. | .. | .. | 1 | 2 | 7 | 4 | 6.0 | 6 |
| Average Intelligence | 35 | A | .. | .. | .. | .. | 1 | 11 | 17 | 6 | 5.8 | 6 |
| | 35 | B | .. | .. | .. | 1 | 1 | 11 | 14 | 8 | 5.8 | 6 |
| Dull average Intelligence | 10 | A | .. | .. | .. | 1 | .. | 5 | 3 | 1 | 5.3 | 5 |
| | 10 | B | .. | .. | .. | .. | 4 | 4 | .. | 2 | 5.0 | 5 |
| Borderline Intelligence | 13 | A | .. | .. | 1 | 3 | 6 | 2 | 1 | .. | 3.9 | 4 |
| | 12 | B | .. | .. | 1 | 3 | 3 | 4 | 1 | .. | 4.1 | 4 |
| Moron | 10 | A | 2 | .. | 3 | 2 | 2 | 1 | .. | .. | 2.5 | 2.5 |
| | 11 | B | 1 | 4 | 1 | 4 | .. | 1 | .. | .. | 2.1 | 2 |

| Diagnosis | No. of Patients |
|---|---|
| Normal | 34 |
| Psychoneurosis | 43 |
| Psychopathic personality | 42 |
| Mental deficiency, moron | 21 |
| Epilepsy and related states | 14 |
| Concussion and head injury | 6 |

None of these patients showed evidence of an acquired impairment of intellectual function. In

the table, "superior" intelligence indicates an intelligence quotient of above 109; "average" intelligence, an intelligence quotient of 90 to 109; "dull average" intelligence, an intelligence quotient of 80 to 89; "borderline" intelligence, an intelligence quotient of 70 to 79, and the "moron" level, an intelligence quotient of 50 to 69, these intelligence quotient scores being computed from performance on the Wechsler-Bellevue intelligence test.

The following observations, based on inspection of the table may be made:

1. A close correlation between intelligence level and performance on the visual retention test is evident.

2. Forms A and B are practically equivalent. For the groups with superior intelligence one finds mean scores of 6, or slightly above 6, and median scores ot 6. The groups with average intelligence make mean scores slightly below 6 and median scores of 6; the groups with dull average intelligence make mean and median scores of about 5, and the groups with borderline intelligence make mean and median scores of 4. The moron groups make mean and median scores of 2.5 or below.

3. Low scores are rarely made by persons of adequate intelligence. Of the 94 subjects of average and superior intelligence, only 1 made a score as low as 3. Conversely, good scores are rarely made by persons of defective intelligence. Of the 21 subjects with mental deficiency, moron level, not a single person attained a score as high as 6.

On the basis of the normative data, the following interpretations have been assigned to the test scores:

| Score | Interpretation |
|---|---|
| 7 | High average |
| 6 | Average |
| 5 | Low average |
| 4 | Subnormal, "borderline" |
| Below 4 | Defective |

*Performances of Patients with Cerebral Lesions.*—One form or the other of the visual retention test was given to a group of 16 patients who were referred for psychologic examination because of suspected mild intellectual impairment associated with an organic pathologic process and in whom positive evidence of impairment of intellectual function of varying degree was found. Of these 16 men, 2 made average scores (6); 5 made low average scores (5), and the remaining 9 made scores below the average range (4 or less). The introduction of the visual retention test into the psychologic examination served a useful purpose in defining the extent and the degree of the impairment. In these cases, the auditory-vocal digit span test, because of its sensitivity to tensional and emotional influences, frequently gave results which were of equivocal interpretive value. These officers and men, most of whom were career men and eager to remain in the Naval service and none of whom showed obvious impairment, typically evinced an attitude of considerable anxiety in their intense desire to do well on the mental tests. On the auditory-vocal digit span test, as on other tests, their postural set tended to be one of marked "concentration" and tension. This attitude, which might possibly facilitate performance on some mental tests, is certainly not conducive to good performance on the digit span test, which requires for optimal performance a certain degree of relaxation and a receptive attitude on the part of the subject. On the other hand, performance on the visual retention test, being relatively insensitive to emotional influences, could be interpreted much more readily. As the normative data show, poor performance on the part of subjects with unimpaired intellectual function is rare. Consequently, a poor performance on the visual retention test, in combination with a poor performance on the digit span test, served to establish the conclusion that a defect in retention of considerable scope did in fact exist, a conclusion which could not justifiably be made on the basis of the digit span performance alone. The combination of a good performance on the visual retention test and a poor performance on the digit span test served to indicate that at least a general defect in retention was not present. If, on the basis of general observation of the patient and of other test performances, the examiner was inclined to doubt the validity of the results of the digit span test, the adequate performance on the visual retention test would support the impression that the retentive capacity of the patient was unimpaired. The combination of a poor performance on the visual retention test and a good performance on the digit span test would indicate that visual retention alone was defective, a type of impairment not infrequently encountered in patients with cerebral lesions. Finally, the combination of adequate performances on the two tests would definitely establish the absence of an immediate memory defect.

In summary, it can be reported that a majority of patients suffering from mild impairment of intellectual function on an organic basis can be expected to show subnormal efficiency on the visual retention test and that the test has shown

itself to be of value in defining the scope of the impairment and in complementing the performance on the digit span test.

## REPORT OF CASES ILLUSTRATING USE OF VISUAL RETENTION TEST [3]

CASE 1.—Application of the visual retention test in the case of a 26 year old Marine recovering from a shrapnel wound in the left parietal area may be noted to indicate how the test can aid in arriving at a judgment concerning the mentality of a patient with a language disorder. At the time of examination the patient no longer showed an overt speech disturbance, although previously he had shown marked anomia and "word-finding" disturbance. At this time he showed an incomplete homonymous hemianopsia, which was rapidly clearing, pronounced acalculia (but no finger agnosia or right-left disorientation) and impairment in reading and writing. His reading was slow, labored and fatiguing. He could not write to dictation but could copy written material. Performance on information and vocabulary tests was average and indicated that the pretraumatic intellectual level had been average, a conclusion in accord with his educational and social history. On the digit span test, he could repeat only 4 digits and reverse only 3 digits. On an "object memory" test, involving the verbal recall of objects which had been exposed to him, his performance was also notably defective. On the basis of the results of these two tests alone one might have concluded that "retentive capacity in general" was considerably impaired and that his mental disabilities extended beyond the language sphere. However, on the visual retention test he made a score of 5, corresponding to a low average performance. Thus, given a retention task in which speech was not involved as the motor element in response, his performance was fairly adequate, a fact which had obvious bearing on the question of whether intellectual impairment was present in addition to the disturbance in the formation, expression and utilization of symbols.

In addition, the results clearly suggested that, although the overt speech disorders (anomia, word-finding disturbance) were no longer apparent, a language disturbance was still present. This, and not defective "basic retentive capacity," appeared to account for the poor performance on the two retention tests involving speech as the motor element in response and symbols as the content of the response. In view of the marked agraphia, the adequate performance on the visual retention test is especially noteworthy.

CASE 2.—A pharmacist's mate, aged 20, sustained a bullet wound in the left frontoparietal region, with immediate flaccid paralysis of the right arm and both legs and complete expressive aphasia for twenty-one days. At the time of psychologic examination, approximately three and a half months after his injury, he showed a spastic right hemiparesis, the paralysis being more severe in the arm than in the leg or face. No sensory disturbances or hemianopsia was present. There was some residual aphasia in the form of hesitant speech and occasional blocking but no receptive aphasia or anomia. Psychologic examination indicated superior pretraumatic intelligence. Performance on tests of arithmetical reasoning and calculation was extremely unstable. One minute the simplest calculation could not be made, and a few minutes later much more difficult calculations would be done readily. Abstract reasoning ability was unimpaired. On the digit span test he could repeat only 5 digits and reverse only 3 digits. On an object memory test, involving the verbal recall of representations of objects seen, performance was defective. However, on the visual retention test, in drawing with the left hand, performance was average (score 6). Two aspects of the performance are noteworthy: 1. As in case 1, the language disturbance evidently led to disturbed performance on retention tests involving speech and containing symbolic material, such as the digit span and the object memory test. The visual retention test, involving drawing as the motor response and containing nonsymbolic material, was done well, indicating the limitation of his defects to the language sphere. 2. Despite the motor defect and the necessity for drawing with the left hand, performance on the visual retention test was adequate, indicating that the scoring standards are sufficiently lenient to insure that the test is in no sense one of drawing ability.

*Performances of Patients with Severe Mental Disorder.*—In this group of 17 patients were included psychotic patients showing impairment of intellectual function, disturbed psychopaths and 2 patients with hysterical pseudodementia associated with amnesia. Performance on the visual retention test was typically poor, only 1 patient achieving an average score (6), 2 patients making a low average score (5) and the rest making scores of 4 or less. The digit span performance of these patients, likewise, tended to be poor.

*Performance of Older Subjects.*—The question whether there is a decline in performance on the visual retention test on the part of older persons has not been systematically studied. Within the age range (17 to 51 years) of the normative group, inspection of the data shows no decline in efficiency with age. To what extent persons in the fifties and sixties would show a decline in efficiency must remain an open question until an adequate sample of that population is investigated. My expectation, based on what is known about the "normal" decline of retentive ability with age, is that persons in the 51 to 60 year age group would show a slight decline in test performance and that persons over 60 years of age would show a more pronounced loss in retentive ability.

*Sex Differences in Performance.*—This question has not been investigated, since the normative group was predominantly male. The 5 women of the group were of either average or superior intelligence, and all made scores within the average range. Significant sex differences in performance on the test are not expected, but this question should be systematically studied.

3. The 2 patients whose cases are reported here are not included in the group of 16 persons with cerebral lesions discussed in the preceding section.

SUMMARY

A brief test of visual retentive capacity, available in two equivalent forms, has been developed for use in the mental examination of patients as a supplement to the auditory-vocal digit span test.

The test involves sensorimotor components which are different from those involved in performance on the digit span test; the material to be retained is of a nonsymbolic nature, and performance on the test is relatively insensitive to emotional and tensional influences.

The normative data indicate a close relationship between the visual retention test score and the level of general intelligence.

Investigation of the performances of patients with cerebral lesions indicates that the test is of value in defining the scope and severity of intellectual impairment.

Normative scores have been developed on the basis of the standardization data, and a manual of directions for administration and interpretation of the test has been developed.[4]

4. The test materials and a manual of directions for constructing, administering and scoring the test are available on request to Dr. A. L. Benton, Student Personnel Bureau, College of the City of New York, Convent Avenue and One Hundred and Fortieth Street, New York.

# Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

## Physiology and Biochemistry

STUDIES ON PALMAR SWEATING. JACOB J. SILVERMAN and VERNON E. POWELL, Am. J. M. Sc. **208**:297 (Sept.) 1944.

Silverman and Powell used a colorimetric technic for measuring sweating of the palms and finger tips. The technic had the advantages of availability, economy, objectivity, practicability and permanence. It consisted in the use of a liberal amount of ferric chloride (25 per cent solution), applied to the area with an ordinary cotton-tipped wooden applicator. The area was then dried thoroughly and contact was maintained for exactly three minutes with a chemically treated paper (5 per cent solution of tannic acid). The tannic acid reacted with iron to form a stain on the paper varying from gray-blue to blue-black. The results are graded from 0, or a faint response, to 3, or an intense response. Palmar sweating is considered under the headings of thermoregulatory, excretory, chemical, axillary, gustatory, spinal reflex and emotional. The authors believe that the palm is one of the few places where emotional sweating takes place and is an indicator of emotional disturbances. Of over 1,100 patients, approximately 25 per cent showed a grade 3 response, and over 80 per cent showed a combined grade 2 and 3 response. Those patients who showed a grade 3, or intense, response revealed evidence of emotional strain or a disturbance of the autonomic nervous system. MICHAELS, M. C., A. U. S.

THE EFFECTS OF ACETYL-BETA-METHYLCHOLINE IN HUMAN SUBJECTS WITH LOCALIZED LESIONS OF THE CENTRAL NERVOUS SYSTEM. STUART M. FISHER and GEORGE W. STAVRAKY, Am. J. M. Sc. **208**:371 (Sept.) 1944.

Fisher and Stavraky studied the effect of the administration of a suitable choline ester to human subjects with localized lesions of the central nervous system. The best results were obtained with intramuscular injections of acetyl-beta-methylcholine chloride. The effects of mecholyl chloride were studied in 12 male patients with lesions of the rostral portion of the cerebral hemisphere or with signs of involvement of the upper motor neurons. Injections of 8 to 25 mg. of mecholyl chloride dissolved in 0.3 to 1 cc. of distilled water were made into the deltoid muscle and were repeated in each patient at least on two or three occasions. Within twenty to thirty seconds after the injection of 8 to 10 mg. of mecholyl chloride normal males experienced a sensation of heat in the face. In 11 patients with lesions of the frontal lobe with or without involvement of the motor cortex, the injection of mecholyl produced an asymmetric response. During the reaction the contralateral extremities were notably colder than the ipsilateral limbs. In cases in which the lesions extended to the motor or premotor cortex, muscular tremors, slight involuntary movements, an increase in spasticity, pronounced hyperreflexia, clonus of the wrist, ankle and patella, and prominence of pathologic reflexes on the opposite side of the body characterized the later stages of the reaction. These effects of mecholyl are interpreted as resulting from a selective sensitization to chemical stimulating agents of partially isolated nerve cells situated in the chains of descending neurons of the brain and spinal cord.

MICHAELS, M. C., A. U. S.

THE INCIDENCE OF BROMISM AT WARREN STATE HOSPITAL. A. ARNOLD KIPPEN, J. Nerv. & Ment. Dis. **99**:968 (Feb.) 1944.

Kippen reviews the literature on the incidence of bromide intoxication in patients admitted to psychiatric hospitals. At the Warren State Hospital bromide determinations were carried out according to the method of Katzenelbogen and Czarski on 1,000 consecutive patients. In 12.3 per cent the level of bromides in the serum was 25 to 400 mg. per hundred cubic centimeters, whereas in 2.6 per cent the bromide level was in the "toxic range" of over 150 mg. per hundred cubic centimeters. Bromide psychoses were present in about one third of the patients with bromide levels in the "toxic range," a total incidence of 0.8 per cent of the series. CHODOFF, Langley Field, Va.

A NOTE ON THE TWO COMPONENTS OF THE DORSAL ROOT POTENTIAL. F. T. DUN and T. P. FENG, J. Neurophysiol. **7**:327 (Nov.) 1944.

Dun and Feng studied the electric potential obtained from one dorsal root in response to the stimulation of another, and distant, dorsal root. The potential was divisible into two parts: The first was unaffected by strychnine but was abolished by section of the dorsal columns between the stimulating and the recording root, and the second was strengthened by strychnine and not affected by section of the dorsal columns. Dun and Feng conclude that the second component is mediated by a number of internuncial neurons.

FORSTER, Philadelphia.

RECEIVING AREAS OF THE TACTILE, AUDITORY AND VISUAL SYSTEMS IN THE CEREBELLUM. RAY S. SNIDER and AVERILL STOWELL, J. Neurophysiol. **7**: 331 (Nov.) 1944.

Snider and Stowell studied the electrical activity of the cerebellum of the cat and monkey and the alterations in this activity produced by tactile, auditory and visual stimuli. Distinct areas were found for the reception of impulses of each modality. Tactile impulses were received (*a*) from the ipsilateral half of the body in the lateral half of the anterior lobe and in adjacent folia and (*b*) from the forefoot and hindfoot of each side in both paramedian lobules, the forefoot having a stronger contralateral representation than the hindfoot. In the anterior lobe and adjacent folia there was an anatomic localization with regional representation. The auditory area was restricted to the lobulus simplex and the tuber vermis. Decerebration failed to affect the auditory responses, but they were abolished by section of the eighth nerve and by destruction of the cochlea or the inferior colliculus. The visual area overlaps the auditory, and the pathways for the visual

responses probably involve the superior colliculus. Full anesthetic doses of sodium pentobarbital did not affect tactile responses but depressed auditory and abolished visual responses. The authors suggest that cerebellar functions are influenced by tactile, auditory and visual stimuli, as well as by impulses from proprioceptors and from the cerebral cortex.

FORSTER, Philadelphia.

SPREADING DEPRESSION OF ACTIVITY IN THE CEREBRAL CORTEX. A. A. P. LEAO, J. Neurophysiol. **7**:359 (Nov.) 1944.

Leao studied the depression of the electrical activity of the cortex of the rabbit under dial anesthesia. The depression resulted from stimulation with a tetanizing current or from mechanical stimulation and spread slowly from the area of stimulation, in all directions, to involve almost the entire cortex. Its development in any one area was gradual, and electrical activity might return to normal in the area of stimulation while distant cortical areas were still in the state of depression. Some regional variations were encountered; thus, stimulation near the occipital pole gave less consistent results than other areas. Electrical stimulation too weak to produce after-discharge produced depression. Two waves of depression could be started simultaneously in distant cortical areas. Treatment of the cortex with cocaine and section or coagulation of the cortex prevented the spread of depression beyond this region. The electrical activity of the opposite hemisphere was also depressed, and the depression of the contralateral hemisphere had its inception at a region symmetric with the stimulated area. Somatic sensory and optic responses were decreased during the depression of the electrical activity of the appropriate area. Motor responses to stimulation were decreased during depression of the electrical activity of the motor area. During depression of the electrical activity of one hemisphere depression of the electrical activity of that hemisphere was also obtained by stimulation of the opposite hemisphere. During the depression of the electrical activity strong repetitive electrical stimuli failed to produce self-continuing electrical responses. The electrical activity due to application of strychnine or acetylcholine could likewise be depressed. During the periods of depression of the electroencephalogram electrical activity differing from the spontaneous activity was frequently observed. This consisted of large, slow negative waves; rapid, spikelike potentials, or activity similar to the tonic-clonic responses of experimental epilepsy. Leao stresses the close relation between the spreading depression and the electrical discharges of experimental epilepsy and indicates that both are probably mediated by the same cortical elements and both are mainly or exclusively cortical.

FORSTER, Philadelphia.

PARALYSIS WITH HYPOTONICITY AND HYPERREFLEXIA SUBSEQUENT TO SECTION OF BASIS PEDUNCULI IN MONKEYS. B. W. CANNON, H. W. MAGOUN and W. F. WINDLE, J. Neurophysiol **7**:425 (Nov.) 1944.

Cannon, Magoun and Windle studied 6 monkeys in whom the right or the left basis pedunculi had been sectioned. The result was a paralysis intermediate between spastic paralysis and hypotonic paresis. They found hypotonicity of all muscle groups except the extensors of the digits, hyperactive deep reflexes and absence of clonus. They conclude that inhibitory pathways descending from the cortex do not all course entirely within the basis pedunculi. The fibers concerned with hypertonicity and clonus have for the most part deviated from the corticospinal projection prior to reaching the cerebral peduncle, whereas the fibers whose interruption leads to hyperreflexia accompany the corticospinal projection in the cerebral peduncle but deviate before reaching the pyramids.

FORSTER, Philadelphia.

THE DEFECT IN UTILIZATION OF TOCOPHEROL IN PROGRESSIVE MUSCULAR DYSTROPHY. ADE T. MILHORAT and W. E. BARTELS, Science **101**:93 (Jan. 26) 1945.

Milhorat and Bartels present a preliminary report on observations on 15 patients with progressive muscular dystrophy. They report that tocopherol (either the free substance or the acetate, phosphate and succinate esters) administered orally was without effect on the creatinuria of their patients except in 1, in whom the dystrophic process was of unusually slow progression. However, tocopherol that had been incubated in the stomach of a normal man lowered the creatine output of about one-half the subjects. A number of other experiments are mentioned, and on the basis of their results and of observations by other workers, the authors postulate requirements for the substance with which tocopherol forms a condensation product in the body. Inositol is one substance which seems to satisfy these requirements. A water-soluble condensation product was prepared by refluxing benzene hexachloride and alpha tocopherol in absolute alcohol containing potassium hydroxide.

Further observations suggest that tocopherol forms a condensation product with inositol in the gastrointestinal tract (tocopherol-inositol ether) and that the defect in muscular dystrophy is a deficiency in the reaction of condensation. The degree of this deficiency appears to determine the rapidity with which muscular disability progresses. Patients in whom the disease process is mild can synthesize sufficient amounts of the condensation product when large amounts of both tocopherol and inositol are given together, but patients in whom the disease is more rapidly progressive will probably require the condensation product itself.

GUTTMAN, Philadelphia.

EXPERIMENTAL EDEMA OF THE BRAIN: I. METHODS OF PRODUCING EDEMA OF THE BRAIN. S. OBRADOR and J. PI-SUÑER, Bol. d. Lab. de estud. med. y biol. **1**:37 (April) 1942.

Obrador and Pi-Suñer used the method of Le Beau and Bonvallet to produce acute edema of the brain. The brain stem was sectioned in the region of the fourth ventricle in adult dogs anesthetized with pentobarbital sodium. Trephine openings in both parietal regions were covered by observation windows. Lesions other than section in the region of the floor of the fourth ventricle also produced pronounced swelling of the cerebral hemispheres. Lesions in the floor of the fourth ventricle causing arterial hypertension were most likely to give rise to cerebral edema. During the experiments it was usually found that the cerebral edema was preceded by a rise in blood pressure. A rise in blood pressure following injury to the floor of the fourth ventricle was not always followed by cerebral edema. Compression of the region of the fourth ventricle usually caused transitory cerebral edema. The edema of the brain was more lasting in almost all the cases than

the rise in blood pressure. Transections in the region of the fourth ventricle caused a more persistent cerebral edema than other lesions in the same region.

SAVITSKY, New York.

## Neuropathology

ENCEPHALITIS AFFECTING THE BASAL GANGLIA IN MONKEYS. RICHARD B. RICHTER, J. Neuropath. & Exper. Neurol. **4**:16 (Jan.) 1945.

Richter reports the pathologic observations in 2 monkeys (Macaca mulatta) with acute encephalitis of unknown origin, presumably spontaneous. One of the animals manifested involuntary movements of choreiform type. Histologic study revealed the presence of focal, bilateral necrotizing lesions confined to the corpus striatum and the globus pallidus. The appearance of chorea in 1 of the monkeys demonstrates that it may occur in the monkey in the presence of bilateral damage to the basal ganglia with an otherwise intact nervous system.

GUTTMAN, Philadelphia.

POREncephaly: II. STUDIES IN PHLEBOTHROMBOSIS AND PHLEBOSTASIS. OTTO MARBURG, P. R. REZEK and M. B. MARKS, J. Neuropath. & Exper. Neurol. **4**:43 (Jan.) 1945.

Marburg, Rezek and Marks report the case of an infant who was delivered by forceps, with bleeding from the left ear and ecchymoses over the body. After a small blood transfusion the bleeding ceased. The clot retraction time was greatly prolonged. At the age of 4 months the child had difficulty with vision, horizontal nystagmus and bilateral optic nerve atrophy. Hydrocephalus was present. At 10 months puncture of a fontanel was performed, which was followed by a septic temperature. Death occurred several days later. A porencephalic cyst was found at autopsy.

The authors conclude that the pathologic process underlying porencephaly is a vascular hemorrhage, thrombosis or stasis in the areas of drainage of the vena magna Galeni or of some cortical veins. The important factor in the pathogenesis is the association of the vascular process with hydrocephalus.

If inflammation causes porencephaly, it does so exclusively through obstruction of the veins, and polioencephalitis does not play a role. Arrested development probably does not cause porencephaly, since the changes considered as evidence of developmental disturbances may be ascribed to venous lesions.

The principal cause of the pathologic changes is trauma: injuries during delivery, particularly instrumental delivery; injury to the fetus by trauma sustained by the mother; injury to the skull shortly before or after birth. Changes in constituents of the blood, although not proved, may serve as a contributing factor.

GUTTMAN, Philadelphia.

CEREBRAL THROMBO-ANGIITIS OBLITERANS AND ITS RELATION TO PERIARTERITIS NODOSA. I. MARK SCHEINKER, J. Neuropath. & Exper. Neurol. **4**:77 (Jan.) 1945.

Scheinker reports 2 representative cases of cerebral thromboangiitis obliterans and 6 cases of periarteritis nodosa. There is a difference of opinion regarding the relation between thromboangiitis obliterans and periarteritis nodosa. Some investigators assume a close connection between the two vascular processes while others do not.

The author states the significant difference between the two conditions as follows: In thromboangiitis obliterans there is a massive proliferation of the subendothelial connective tissue, with consequent narrowing or occlusion of the vascular lumen. In periarteritis nodosa minimal secondary intimal proliferation may be observed, and then only occasionally in the final stage of the disease, when it is always associated with periarteritis. In thromboangiitis obliterans the proliferative changes are never, or are seldom, complicated by inflammatory or advanced necrotic changes. Severe inflammatory changes of the entire vascular wall, associated with necrosis of the subendothelial connective tissue and the adjacent media, are the primary and the most characteristic lesions of periarteritis nodosa. Marked degeneration of the internal elastic membrane, represented by disruption and splitting of fibers with eventual complete necrosis, is frequently observed with periarteritis nodosa, but is seldom seen with thromboangiitis obliterans. In periarteritis nodosa the pathologic changes involve the entire vascular wall; in thromboangiitis obliterans the lesions are usually confined to its inner layer. The frequently observed intramural hemorrhages in the early stage of thromboangiitis obliterans are not seen with periarteritis nodosa.

Scheinker offers the hypothesis that the characteristic early lesions of thromboangiitis obliterans may be reversible circulatory disturbances (angiospasm and vasoparalysis), which may become irreversible if of prolonged duration or repeated occurrence. The view is expressed that each of these vascular diseases has a characteristic morphology and that pathologically they should be considered as different vascular syndromes.

GUTTMAN, Philadelphia.

A REVIEW OF SOME RECENT OBSERVATIONS ON DEMYELINATION. E. WESTON HURST, Brain **67**:103, 1944.

Hurst reviews the developments in the understanding of the process of demyelination, considering them under the various hypotheses regarding the causation of demyelination. He considers in detail the evidence for the role of vascular blocking in the causation of demyelination and points out that demyelination with degeneration of axis-cylinders may result from a relatively minor obstruction of the circulation in the white matter without progression to complete necrosis. While obstructing plugs in experimental procedures may disappear rapidly after resulting in a lesion, there is no present evidence that the same factor may be present in the human brain. In reviewing the observations on the effects on the brain of chemically induced anoxia, Hurst concludes that the anoxia may be followed, according to its severity and duration, by cerebral lesions varying from cortical necrosis to demyelination of the white matter. The cortex has a greater need for oxygen, while the white matter has less recuperative power, so that a single period of less intense anoxia or a repetition of minor insults may lead to severe involvement of the white matter. As to the production of demyelination by the action of antibodies on brain tissue, Hurst reviews the work of Ferraro and Jervis and their successful production of demyelination in monkeys by this method. Hurst was unable to produce this process in other species. He points out the paucity of experimental evidence pointing to an allergic basis for demyelination. He attempted, unsuccessfully, to induce demyelination in animals with egg albumin but concludes that further study is neces-

sary to evaluate the role of antigen-antibody reactions and the responses of antibodies to brain tissue. The author points out that in the distemper of dogs the virus may be responsible for demyelination. Biochemical studies in the demyelinating diseases have been concerned with the myelolytic effect of plasma, serum or urine in vitro on the spinal cord of animals or the demonstration of various abnormal enzymes in the serum.

Hurst notes the wide diversity of agents which produced demyelination experimentally and the association between necrosis and demyelination in the same case or the replacement of demyelination by necrosis with an increase in the intensity of the pathologic agent. He concludes that demyelination is the response of the white matter to injuries short of lethal and suggests that attempts to find a single causative agent for demyelination will be unprofitable.

FORSTER, Philadelphia.

CHANGES IN THE BRAIN IN ALCOHOLIC PSYCHOSES. D. NIETO, Bol. d. Lab. de estud. med. y biol. **1**:57 (May) 1942.

Nieto reports unusual histopathologic changes in 2 adults who died during attacks of delirium tremens. No other cause for death was found. A marked increase in oligodendroglia was found in the subependymal and periaqueductal regions and about the third ventricle. In the surrounding area there was evident gliosis. The changes in the frontal regions were similar to those encountered in 6 cases of psychosis with pellagra. The subependymal proliferation of oligodendroglia is considered a reaction to toxins which appear in the spinal fluid during the course of delirium tremens.

SAVITSKY, New York.

## Psychiatry and Psychopathology

INTELLECTUAL IMPAIRMENT IN HEAD INJURIES. JURGEN RUESCH, Am. J. Psychiat. **100**:480 (Jan.) 1944.

Ruesch studied the frequency and nature of intellectual impairment following head injuries. The following psychometric tests were found to be most efficacious in measuring the impairment: 100-7 test, pictorial absurdities, hole in the board test, pictorial discrimination, naming of colors and reading. The primary deficits were found to be in speed, judgment and ability to maintain sustained effort. These defects were evaluated in two ways: (1) by comparison of performance with estimated intelligence and (2) by improvement on repeated examinations.

Ruesch found intellectual impairment of slight degree in approximately one half of all subjects with head injury. With the passage of time these defects decreased in severity. Reversible impairments usually did not persist more than three months. The degree of mental impairment could be correlated to some extent with the degree of organic cerebral damage.

FORSTER, Philadelphia.

THE PSYCHONEUROSES OF WAR. J. L. HENDERSON and MERRILL MOORE, New England J. Med. **230**: 273 (March 9) 1944.

Henderson and Moore analyze a series of 200 cases of neuropsychiatric disorders in patients admitted to a military hospital in the South Pacific. They report that about 23 per cent of all patients admitted to hospitals presented neuropsychiatric problems. In 49 per cent of this number, the disorder was diagnosed as anxiety neurosis; in 20 per cent, as hysteria; in 7 per cent, as constitutional psychopathic state; in 6 per cent, as schizophrenia; in 5 per cent, as manic-depressive psychosis; in 4 per cent, as epilepsy, and in 9 per cent, as miscellaneous disorders. Almost all patients reported having a broken home or neurotic parents. Thirty per cent gave a positive history of head injury prior to induction. Thirty-five per cent had previously experienced a sudden or overwhelming trauma, such as an automobile accident. Of the last group, many had lost consciousness and suffered amnesia, as well as hysteria. These reactions recurred during bombings and shellings.

Loss of weight in the battle zone averaged roughly 21 pounds (9.5 Kg.) per patient, and polyneuritis, probably due to vitamin deficiency, was present in a number of patients. Twenty-five per cent of the patients had malaria, and 12 per cent suffered from organic cerebral damage resulting from bomb or shell blast.

Fatigue and the intensity, as well as the repetition, of traumatic experiences in the combat zone enhanced the psychoneurotic state. Those who "broke" earliest had the poorest prognosis. The chief predisposing factor was the neurotic makeup of the patient. Nightmares were an almost universal symptom in the group and were associated with concomitant reactions of the sympathetic nervous system. The nightmares usually were repetitive dreams of combat. The patients recounted these dreams to each other, apparently for catharsis, and derived some relief therefrom.

Bombing and shelling precipitated neuroses. The experience of hiding in a foxhole or other shelter subjected to enemy attack without being able to fire back was particularly unbearable, since no release from tension could be afforded by physical activity. This enforced passivity resulted in physical, as well as mental, symptoms and often recurred as the characteristic nightmare pattern.

Many of the patients were found to have had a mutually overdependent relationship with their parents. Their resultant inability to express normal hostility proved a serious handicap in the battle situation. There were frequently overidentification with the mother and fear of an abusive father.

Limitations of time restricted attempts at therapy. Sedation was the quickest approach for the relief of surface symptoms. Some occupational therapy was tried, with success. Hypnosis was also useful. In addition group psychotherapy was employed, with the therapeutist giving a necessarily superficial explanation of symptoms, as well as encouragement. The authors believe, however, that the only lasting therapy is of the individual type, although this was not practicable in the war situation.

GUTTMAN, Philadelphia.

SUBLIMATION. GÉZA RÓHEIM, Psychoanalyt. Quart. **12**:338, 1943.

Róheim believes that sublimation has three associated sources. A neurosis is the repetition of an infantile tragedy, while sublimation is the repetition of a happy infantile situation, of a traumatic situation that has been mastered successfully. In a neurosis the conflict between the superego and the ego ends in defeat of the latter. The ego pleads guilty and enters a state of perpetual mourning. The basic element of a neurosis is melancholia. In sublimation and cultural activity the ego, allied with the id, is victorious and controls the

superego. The basic element is mania. A third source of sublimation lies in the process of growth, which decreases the initial helplessness of infancy and forms the basis of the ego. Here ego and id are acting in harmony, and the superego is absent. Sublimation is a sublimation of the erotic drive and is a substitute for coition or some other type of libidinal activity. A sublimation is always based on an infantile erotic activity or fantasy. Although the superego always represses the id strivings in sublimation the id strivings reconquer the ground in a disguised form.

The neurotic part of the personality is the past; the maturation or stimulus reaction part is the present. Sublimation, although based on the past, stands for the future, or the assurance of a future of "Paradise Regained."

PEARSON, Philadelphia.

## Meninges and Blood Vessels

ACUTE MENINGOCOCCAL ENCEPHALOMYELITIS. WILLIAM B. WARTMAN and IRWIN C. HANGER, Am. J. M. Sc. **208**:234 (Aug.) 1944.

Wartman and Hanger report the case of a white man aged 27 who was admitted to the hospital complaining of headache, backache and fever, which had been steadily increasing for twenty-four hours. The temperature was 101 F., and the pulse rate was 116 per minute. There was questionable stiffness of the neck, which at the time was attributed to the severe headache. Three days after admission he became irrational and was given 10 cc. of paraldehyde intravenously. The spinal fluid was grossly purulent and contained 54,900 leukocytes, mostly neutrophils, per cubic millimeter. After a stormy course, the patient died, four days after admission. The clinical diagnosis was acute cerebrospinal meningitis due to meningococcus and bronchopneumonia involving the lower lobe of each lung, of undetermined cause. Study of the central nervous system revealed a delicate film of creamy yellow pus which occupied the sylvian fissure and the sulci on the lateral and superior aspects of the brain. The dura mater was hyperemic. The cerebral hemispheres were greatly swollen. Numerous clusters of bright red, punctate hemorrhages were scattered throughout the white matter, but the gray matter was mostly spared. The tissues were extremely edematous and hyperemic, with wet, boggy, pink cut surfaces. Throughout the white matter of the entire spinal cord were numerous small hemorrhages, similar to those in the brain. All parts of the lungs were extensively consolidated, except for a few small foci at the apex and along the lower margin of the upper lobes. The microscopic examination revealed hemorrhagic, as well as inflammatory, lesions throughout the white matter of both cerebral hemispheres. They were most common in the posterior frontal, parietal and anterior occipital regions. Although clinically the condition was thought to be meningococcic cerebrospinal meningitis, autopsy revealed acute encephalomyelitis, violent and extensive, with but comparatively little meningitis.

MICHAELS, M.C., A.U.S.

MENINGOCOCCIC MENINGITIS IN SANTIAGO, CHILE, 1941 TO 1943: AN EPIDEMIC OF 4,464 CASES. ABRAHAM HORWITZ and JOSE PERRONI, Arch. Int. Med. **74**:365 (Nov.) 1944.

Horwitz and Perroni report that an epidemic of meningococcic meningitis started in the port of Valparaiso in June 1941 and extended from there until it reached Santiago, a distance of about 80 miles, three months later. The total number of cases recorded in Santiago from September 1941 to July 3, 1943 was 4,464. The incidence was approximately 1 case per 300 inhabitants, and the largest number of cases occurred in 1942. The disease was slightly more common in males than in females and was more fatal in infancy and old age than in the other periods of life. The fatality rate for all patients was 16.5 per cent; for infants under 4 years it was 28 per cent.

In a series of 450 unselected patients treated with sulfonamide compounds, the mortality was 9.3 per cent with sulfadiazine therapy, 10.7 per cent with sulfathiazole therapy and 13.3 per cent with sulfanilamide therapy. Toxic reactions occurred in 33 per cent of patients who received sulfanilamide and in 4.4 per cent of the patients who were given sulfadiazine.

GUTTMAN, Philadelphia.

MENINGOCOCCAL MENINGITIS AND MENINGOCOCCEMIA IN CHILDHOOD: A STATISTICAL STUDY OF SEVENTY-TWO CASES. JOSEPH OSBORNE, WILLIAM H. ARNONE and GEORGE I. LYTHCOTT, New England J. Med. **231**:868 (Dec. 28) 1944.

Osborne, Arnone and Lythcott report observations on 72 children, all under 12 years of age, who were treated for meningococcic meningitis or meningococcemia.

The onset was acute in 59 per cent of the cases and was ushered in by nausea and vomiting in 64 per cent, by headache in 31 per cent, by stiff neck in 17 per cent, and by a cutaneous rash and drowsiness in 14 per cent. The lesions of the skin were a valuable aid in the diagnosis of meningococcemia and were present in 82 per cent of the cases at the time of admission. The other chief complaints were as follows: convulsions, 11 per cent; fever, 10 per cent; delirium, 10 per cent; abdominal pain, 6 per cent; arthralgia, 3 per cent; myalgia, 4 per cent, and coma, 3 per cent. Convulsions were limited almost entirely to patients under 3 years of age. They occurred in 10 of the 14 children 1 year of age, in 4 of the 12 children 2 years of age and in 2 of the children 7 years old. Of the patients over the age of 3 only 1 had a convulsion.

The predominant type of organism was a type 1 meningococcus, occurring in 76 per cent of the cases in which the cultures were positive. All the patients were treated with sulfadiazine.

The most frequent complication was arthritis, occurring in 12 per cent of the cases. This was a periarthritis without active suppuration within the joint. The average time for the appearance of manifestations in the joints was six days after the onset of the disease. The symptoms persisted for about eight days. The treatment was immobilization, followed by passive motion and physical therapy as soon as the active inflammation subsided. Complete recovery from the arthritis occurred in all cases.

The mortality rate was 8 per cent, the meningitis in all but 1 of the 6 fatal cases being of the Waterhouse-Friderichsen type. Four children with this syndrome survived.

GUTTMAN, Philadelphia.

HIGH ALTITUDE FROSTBITE. LOYAL DAVIS, JOHN E. SCARFF, NEIL RODGERS and MERIDETH DICKINSON, Surg., Gynec. & Obst. **77**:561 (Dec.) 1943.

High altitude frostbite differs from ordinary frostbite in that it is caused by extreme degrees of cold (—40

to —52 C.), usually lasting only a few minutes, and is associated with varying degrees of anoxemia and ischemia of the extremities. It has a special predilection for the extremities.

The mild form follows the briefest removal of a glove at high altitude, the fingers becoming painfully cold, numb, waxy white and completely insensitive to touch. Recovery after removal to a warmer environment may be slow. Several hours may be required for the fingers to soften, and even then the white, ischemic color may persist for several hours longer. No permanent ill effects result, but paresthesias may persist for days or weeks.

The severe types consist of a wet and dry form and follow more prolonged exposure to cold. The wet form is characterized by multiple small cutaneous blisters appearing simultaneously on the affected part, which rapidly coalesce. These large blisters may contain free fluid, but more often the excessive fluid is held fast in the tissue composing the superficial layers of the skin and resists aspiration by needle and syringe. The blister dries in two to three days, the superficial layers of the skin becoming loose and wrinkled, then dry and hard, finally being thrown off, often as a complete cast of the part. The regenerated skin is shiny and varies in color from dusky pink to dusky blue, the color changing with the temperature of the environment. The part is sensitive to cold, and tolerance to cold is considerably reduced. Anesthesia or hypesthesia and analgesia or hypalgesia may persist for months. Loss of sweating of the part parallels the sensory loss.

The dry form usually results after even more extensive exposure. Instead of the formation of blisters, the finger or hand becomes tense, and the skin assumes a dull, ground glass appearance. The affected part then darkens, and all the tissues shrivel and mummify. Spontaneous amputation occurs in two to three weeks. The proximal phalanx of the finger is never involved unless more distal ones are also affected. The outstanding characteristic of this type of frostbite consists of the selective action on the fingers or toes, with sparing of the face, even if exposed for hours. Direct examination of terminal capillary loops in the finger indicates that acute selective vasoconstriction of the peripheral arterioles is the responsible factor, since the terminal arterioles are well filled with blood while the capillary loops are empty. The first effect of the cold is to damage the endothelium and to increase its permeability, thus permitting an extravasation of plasma or blood, which leads to the wet type of frostbite. More severe damage of the endothelium causes thrombosis, usually at the arteriolocapillary junction, which, then, is the basis of the clinical picture of dry gangrene.

Prophylaxis for this type of injury rests in good measure on the engineer, to prevent as far as possible exposure to cold and risks of general anoxemia. Treatment is still in the investigative stage. It is the authors' opinion that maintaining the affected part at room temperature yielded better results than continued, controlled cooling and gradual thawing of the part. Cooling caused less blistering, but a group so treated complained of more pain and ultimately lost more tissue than the patients exposed immediately to room temperature. Attempts to increase the peripheral blood flow by use of amylnitrite, alcohol, acetylsalicylic acid or glyceryl trinitrate, contrary to expectation, resulted in failures to increase the cutaneous temperature in the extremities tested. Sympathetic block was effective in relieving the peripheral vasoconstriction and in raising the cutaneous temperature of the affected digits in cases of mild frostbite but was entirely ineffective in cases in which thrombosis had already occurred.

SHENKIN, Philadelphia.

CHEMOTHERAPY OF INTRACRANIAL INFECTIONS: V. THE TREATMENT OF STAPHYLOCOCCIC AND PNEUMOCOCCIC MENINGITIS WITH SULFATHIAZOLE AND SULFADIAZINE. W. F. MEACHAM, E. SMITH and C. PILCHER, War Med. **6**:378 (Dec.) 1944.

The authors report the results of treatment of staphylococcic and pneumococcic meningitis in 152 experimental animals with the use of sulfathiazole and sulfadiazine. They found that sulfadiazine was present in much greater concentration in the cerebrospinal fluid after oral administration than was sulfathiazole. Experimental staphylococcic meningitis was not benefited by the oral use of sulfathiazole. The oral administration of sulfadiazine was distinctly beneficial in the treatment of staphylococcic meningitis in dogs. Experimental staphylococcic meningitis was not benefited by the intracisternal administration of suspensions of microcrystalline sulfadiazine. This method of therapy is believed to be harmful. The oral administration of sulfadiazine was decidedly beneficial in the treatment of pneumococcic meningitis. A high concentration of sulfadiazine in the cerebrospinal fluid was found to be essential to recovery in the experiments on pneumococcic meningitis.

PEARSON, Philadelphia.

MENINGITIS DUE TO PS. PYOCYANEA: PENETRATING WOUNDS OF THE HEAD. E. H. BOTTERELL and D. MAGNER, Lancet **1**:112 (Jan. 27) 1945.

Botterell and Magner report a series of 11 cases of meningitis due to Pseudomonas aeruginoso (pyocyanea), in 9 of which death resulted. The patients were men with wounds of the head who were evacuated from France to a neurosurgical hospital in England. In 2 cases it is believed on clinical and pathologic evidence that the intrathecal injection of contaminated penicillin might have been the source of the meningitis. In 9 cases infection of the cerebral wound is believed to have spread to the subarachnoid space or the ventricular system. In 4 of the first 9 cases, the meningitis was secondary to cerebral abscess, and it seemed likely that Ps. aeruginosa was present before admission in 3 of the cases. Cultures in another case yielded organisms from temporal muscle adjoining the subarachnoid space. The source of infection in 4 cases seemed to be cross infection in the hospital, attributed in 3 cases to a tube being left in the wound for the repeated instillation of penicillin.

The authors conclude that the risk of meningitis due to Ps. aeruginosa is minimized by complete débridement and primary closure of penetrating wounds and by avoidance of placing of tubes in wounds for the introduction of penicillin. The intrathecal injection of penicillin should be restricted to the treatment of meningitis; in prophylaxis it should be used with caution. For intrathecal use the authors recommend that penicillin be issued in bottles containing only sufficient solution for single injections.

YASKIN, Camden, N. J.

## Diseases of the Brain

DIFFUSE NEUROFIBROMATOSIS (VON RECKLINGHAUSEN'S DISEASE) INVOLVING THE BULBAR CONJUNCTIVA: REPORT OF A CASE, WITH LESIONS OF THE SKELETAL SYSTEM AND SKIN, BODILY ASYMMETRY AND INTRACRANIAL INVOLVEMENT. FRANCISCO PÁEZ ALLENDE, Arch. Ophth. **33**:110 (Feb.) 1945.

Neurofibromatosis of the nerves of the periosteum of the orbit may cause subsequent erosion and invasion of the osseous wall, or there may be erosion or thinning of the bones through the mechanical effect of pressure on the part of the tumor. Three clinical forms of neurofibromatosis may exist: (1) predominant invasion of the central nervous system (intracranial organs); (2) predominant invasion of external structures (skin), and (3) involvement chiefly of the skeletal system.

When the ocular apparatus and the ocular adnexa are affected, the parts most frequently attacked are, first, the eyelids and the optic nerve, followed by the orbit, the retina, the iris, the cornea, the tarsal conjunctiva and, finally, the bulbar conjunctiva.

The study of the case reported revealed: (1) twinship, (2) coexistence of neurofibromatosis and epilepsy, (3) bodily asymmetry, (4) intracranial disorders, (5) skeletal lesions, (6) cutaneous tumors, (7) partial alopecia of the scalp on the side of the affected eye and (8) slight mental retardation.

SPAETH, Philadelphia.

TOXOPLASMOSIS: REPORT OF OCULAR FINDINGS IN INFANT TWINS. PARKER HEATH and WOLFGANG W. ZUELZER, Arch. Ophth. **33**:184 (March) 1945.

Toxoplasmosis is a recently recognized infectious disease in human beings. Four principal types have been reported: (1) a granulomatous encephalitis, usually of congenital origin and occurring in fetal or early infantile life; (2) an acquired acute encephalitis, occurring in children; (3) an acquired acute disease resembling Rocky Mountain spotted fever, occurring in adults, and (4) a latent subclinical form, occurring in adults.

Heath and Zuelzer report the ocular changes associated with the disease in premature identical Negro twins. The symptoms appeared on the third day after birth. One of the babies died at the age of 1 month. The histopathologic observations on this twin are presented in detail. The second infant lived and was followed through the seventh month after birth. These 2 cases, in which the ocular lesions were so characteristic of toxoplasmosis, gave opportunity for study of the changes seen with the ophthalmoscope in identical twins.

SPAETH, Philadelphia.

THE CEREBROSPINAL FLUID IN METASTATIC BRAIN TUMORS. EDWARD W. SHANNON and CLINTON W. MORGAN JR., New England J. Med. **231**:874 (Dec. 28) 1944.

Shannon and Morgan report on determinations of the protein content of the lumbar cerebrospinal fluid in 43 patients with metastatic intracranial neoplasms. The average protein value was 99 mg. per hundred cubic centimeters. Ninety-one per cent of the patients had a protein value of 40 mg. The highest protein content was found in patients who had superficial cerebral metastases. When supratentorial metastases were present the protein content of the lumbar cerebrospinal fluid was greater than that found in the presence of infratentorial lesions.

The authors conclude that the protein content of lumbar cerebrospinal fluid alone does not differentiate a metastatic neoplasm from a primary tumor of the brain.

GUTTMAN, Philadelphia.

ONE ASPECT OF THE POSTTRAUMATIC SYNDROME IN CRANIOCEREBRAL INJURIES. KENNETH G. MCKENZIE, Surg., Gynec. & Obst. **77**:631 (Dec.) 1943.

McKenzie proposes the hypothesis that the vasomotor system is injured in craniocerebral accidents and is unable to regulate the supply of blood to the brain and that post-traumatic complaints of dizziness, light-headedness, black-outs, headache and mental and physical fatigue result. A case is cited of a young man who six months after a head injury and a period of unconsciousness lasting one-half hour complained of persistent incapacitating headache and dizziness. The dizziness proved to be faintness or light-headedness on change from the horizontal to the erect position. The systolic pressure was 120 mm. of mercury with the patient in the horizontal position; in the standing position the pulse disappeared at the wrist, and the patient became white and nearly fainted. Adaptation to the new position required a few moments. Sleeping with the shoulders and head up and practice in stooping exercises resulted in complete relief from symptoms in three months.

The author now has patients sitting up and out of bed as soon as possible after an injury to the head, usually in a few days. This, he feels, more quickly retrains the injured vasomotor system to meet the demands of variation in posture. In addition, early mobilization of the patient indicates that progress is being made and minimizes the effects of the injury to patient and relatives, thereby having a favorable psychologic influence on the situation. The author further suggests that hospitalization be prolonged for patients with post-traumatic complaints of this nature and that active treatment be carried out. Such therapy consists of stooping exercises, games requiring changes of position and occupational therapy, all given with a view to retraining the vasomotor system.

SHENKIN, Philadelphia.

DEJERINE-ROUSSY SYNDROME CAUSED BY GUNSHOT WOUND: REPORT OF A CASE. PEDRO I. LANZANI and F. DE GREGORIO LAVIÉ, Prensa méd. argent. **46**:2338 (Nov.) 1944.

The authors report the second case of thalamic hyperesthetic anesthesia, or the Dejerine-Roussy syndrome, caused by a gunshot wound. A 20 year old Argentinian woman was admitted in a state of shock with two gunshot wounds, one bullet lodging in the region of the third cervical vertebra and the other entering the left frontoparietal region and lodging finally in the left occipital region. On the fourth day, aphasia was noted, and the right corneal reflex was diminished. On the eighth day the disks were blurred. In about three months a hemisensory syndrome was found on the right side, with absence of the plantar response on that side. There were also some alexia and agraphia. Two months later, headache and dizziness were intense, and the patient became excited. Bilateral papilledema was found, with pronounced diminution of vision in the right eye. Taste, smell and hearing sensations were diminished on the right side. There was dystereognosis on the same side, as well as global aphasia. The patient was operated on four months after the injury, and a temporal decompression

was done on the right side. The signs of increased intracranial pressure disappeared. There was no real thalamic pain, and no thalamic dysesthesias were noted. At the end of nine months there was no longer motor weakness and the aphasia had disappeared; there was diminished sensation on the right side of the body, with sensory changes in the first division of the left fifth nerve.

SAVITSKY, New York.

## Encephalography, Ventriculography, Roentgenography

ROENTGENOLOGIC MANIFESTATIONS AND CLINICAL SYMPTOMS OF RIB ABNORMALITIES. HOWARD A. STEINER, Radiology **40**:175 (Feb.) 1943.

Steiner studied 38,105 roentgenograms of the spine, chest and abdomen. Among this number were 59 (0.15 per cent of the total) with abnormalities of the ribs. These anomalies are classified as follows: (1) cervical ribs; (2) lumbar ribs; (3) bipartition of ribs or forking of the anterior end; (4) synostosis, or bony union of adjoining ribs; (5) "tile roof" ribs, or imbrication of ribs; (6) rudimentary ribs, and (7) other deformities.

Nineteen cases of cervical ribs, or 32 per cent of the 59 cases, were noted. In all these the anomaly was associated with the seventh cervical vertebra. In 2 cases the condition was bilateral. The average length of the cervical ribs on the right side was slightly greater than that of the ribs on the left (44.4 mm., as compared with 37.5 mm.). The longest cervical ribs were of the joined type, and their incidence was about equal to that of the unjoined ribs.

The association of roentgenographic evidence and of symptoms was stated as follows: (1) very positive correlation; (2) slightly positive correlation, and (3) negative correlation. The chief complaint was pain, which was present as a positive correlation in 10 cases, or 52.6 per cent. In 6 cases the pain was localized to the back of the neck, and in 4 cases it was referred to the shoulder or to the supraclavicular region. No instance of neuromuscular disturbance of the hands or arms was noted. In 3 cases, or 15.9 per cent, vague pain was localized to the shoulder joint, suggestive of bursitis. In the remaining 6 cases, or 31.5 per cent, no symptoms were referable to the cervical ribs. Thus, in 68.5 per cent of the cases of cervical rib symptoms were associated with the anomaly. Age appeared to be of no significance. Two thirds of the patients were females.

Seventeen cases of lumbar rib were found, the condition being bilateral in all but 1 case. All of these were associated with the first lumbar vertebra. In 12 cases the anomaly was associated with symptoms, backache, of varying degrees of severity, being complained of in all. As in the cases of cervical rib, there was a predominance of females (12 females to 5 males).

In 5 cases bifurcation of the ribs was present; in 2 cases the first ribs were involved and in 2 the fourth ribs. In 1 of the cases an apical tuberculous lesion was demonstrated. Schedtler found that abnormalities of the first rib predispose to apical tuberculosis. Four, or 80 per cent, of the patients with this abnormality were males.

Synostosis was present in 5 cases. In 3 cases the union was between the first and the second rib; in 2 cases a tuberculous lesion was present in the apex of the lung behind the synostosis. In the other 3 cases there was no correlation of symptoms. All 5 patients were males.

"Tile roof" formation, or imbrication of the ribs, was present in 4 cases, in 3 of which the condition was bilateral. In 3 of the 4 cases pneumonia or tuberculosis was the chief clinical symptom. In the fourth case there was a chronic cough but no definite pulmonary lesion. Three of the patients were males.

In 5 cases a rudimentary rib was found, the anomaly being always confined to the first rib. In 3 cases the lesion was bilateral. No symptoms were associated with this abnormality. Four of the patients were males.

In 4 cases other deformities not falling into the preceding classification were observed, all of different types. None of them were associated with symptoms.

KENNEDY, Philadelphia.

DEVELOPMENTAL THINNESS OF THE PARIETAL BONES. JOHN D. CAMP and LEO A. NASH, Radiology **42**:42 (Jan.) 1944.

The authors discuss the salient features of parietal thinness on the basis of a study of 119 cases. This condition, known to anatomists and pathologists, escaped the attention of roentgenologists until 1910.

Two types of parietal thinness of the skull are seen in the posteroanterior projection—the flat and the grooved. The thinness is greatest at the center of the lesion and decreases as the periphery is approached. The defect is primarily in the diploe, while the outer table is thinned and depressed. The authors, contrary to previous case reports, did not find the inner table affected. In their series, this anomaly was found in 0.46 per cent of all examinations. In the 119 cases, the condition was bilateral in 107, of the flat type in 106 and of the grooved type in 13. In 80 cases females were affected, and the average age was 56; 10 of the patients were under 30 years of age.

No clinical symptoms could be attributed to the lesion of the skull. The cause is unknown, being most likely a diploic dysplasia of developmental origin.

The importance of parietal thinness lies only in differentiating it from somewhat similar-appearing conditions of the skull. Developmental thinness of the parietal bones is unrelated to enlarged parietal foramens.

TEPLICK, Philadelphia.

# Society Transactions

## BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

PAUL I. YAKOVLEV, M.D., *Presiding*

*Regular Meeting, Nov. 16, 1944*

**Capillaries of the Finger Nail Folds in Cases of Neurosis, Epilepsy and Migraine.** DR. ALFRED HAUPTMANN.

I have examined 125 normal persons, 375 neurotic patients, 117 epileptic patients, 37 patients with migraine headache, 21 patients with nonmigraine headache and 28 patients with other neurologic diseases for the morphologic characteristics of the capillaries of the finger nail folds.

Ninety-three per cent of the normal persons had normal capillaries; 7 per cent showed abnormalities of the capillaries such as are seen in neurotic persons. Normal capillaries are hairpin-like; there is visible no subpapillary network of vessels and the network characteristic of the early development of the capillaries in newborn children, and found also in mentally retarded children, is not present.

Eighty-eight per cent of the patients with constitutional neuroses showed abnormal capillaries, and 11.9 per cent only had normal capillaries. On the other hand, of persons with neurotic reactions, that is, with an acquired neurosis, only 4.3 per cent had abnormal capillaries and 95.7 per cent normal capillaries. The most frequent morphologic abnormality of the capillaries was tortuosity. Another abnormality was the unequal distribution of the capillaries in one horizontal line. The corium papillae was not well scalloped. In a small percentage of patients an immature picture, observed in children prior to the final development of the capillaries, was noted. Of 586 subjects, (normal subjects, neurotic patients, patients with nonmigraine headache and persons with other neurologic diseases), this percentage did not exceed 12.4. Patients with anxiety neuroses exhibited the highest percentage of abnormal capillaries. Patients with hysteria had the most immature capillaries.

Thus, the capillary picture permits to a certain extent the differentiation of constitutional neurosis and neurotic reactions (acquired neurosis). It might be a welcome aid in detecting neurotic persons in a group of so-called normal persons, e. g., would-be soldiers at the induction center, employees for special branches in which a stable personality is required or school children.

Of the 117 epileptic patients, 68.4 per cent of the 73 with idiopathic epilepsy showed a horizontal network of vessels in the area proximal to the end row capillaries, whereas only 22.7 per cent of patients with symptomatic epilepsy showed this pattern. This picture must be interpreted as one of immaturity, as standstill in the development of the capillaries before the end point is reached. The fact that the figures are not higher than 68.4 per cent or lower than 22.7 per cent can be explained partly by the difficulty in distinguishing between idiopathic and symptomatic epilepsy and partly by the probability that some of the patients with symptomatic epilepsy actually had potential idiopathic epilepsy. This capillary picture is not absolutely characteristic of epilepsy, since some neurotic persons, and even some normal persons, show the same pattern; however, the low percentage (12.4) found in those people differs widely from the high percentage (68.4) for the epileptic patients.

I should not say that the presence of a horizontal network of vessels is a positive diagnostic aid in questionable cases of epilepsy; however, the absence of this pattern speaks strongly against the presence of idiopathic epilepsy.

Of the patients with migraine, 54 per cent showed the same picture as did epileptic patients, whereas none of the patients with nonmigraine headache had this kind of picture. These findings support the view that epilepsy and migraine are related.

Functional alterations of the capillaries, changes in the blood flow due to emotional stimuli, to hyperventilation, to drugs or to smoking, have been studied in addition to these morphologic abnormalities and will be reported on later.

DISCUSSION

DR. FELIX DEUTSCH: I consider this investigation important, especially with respect to epilepsy. I wish to ask a few questions about the findings in the neurotic patients. In the patients with neurosis on a constitutional basis, what primary changes in the capillary formation should be looked for? Dr. Hauptmann was interested only in the formation of the capillaries and did not discuss the functional behavior of the capillaries. One can find fairly normal capillaries with abnormal function. Therefore, when one examines a neurotic patient, one is concerned not only with the form but with the behavior of the capillaries. In patients with hysteria one finds a primary disturbance, an arrested development, of the capillaries. In patients with obsessional neuroses this functional behavior is not observed so regularly. Why is it necessary to call so much attention to the behavior of the subcapillary plexus? It indicates an arrested development. Secondary formative disturbances must also always be taken into consideration. During life the capillaries may undergo various formative changes; for instance, aged people or people who have high blood pressure may show secondary changes in the capillaries. Therefore, one must always consider what sicknesses the patient had or what drugs he has taken in the past. I want to stress the fact that the formation of the capillaries is not enough for evaluation of their relation to a neurosis but that their behavior must also be examined.

DR. D. DENNY-BROWN: I should like to ask Dr. Hauptmann whether he has observed any relation between these changes in the capillary plexus and the growth of the nails; perhaps this plexus has some relation to the underlying nail bed.

DR. WILLIAM G. LENNOX: Paskind and Brown compared the capillaries of deteriorated and of mentally normal epileptic persons (Constitutional Differences Between Deteriorated and Nondeteriorated Patients with Epilepsy, ARCH. NEUROL. & PSYCHIAT. **49**:49 [Jan.] 1943). The greater distortion of capillaries in the deteriorated group was ascribed to constitutional inborn differences. I wonder whether the form of the capillaries is a hereditary trait. If so, it would be of interest to compare the capillaries of the parents of

these epileptic patients, as well as the loops of identical twins when only one has epilepsy. What about brain waves? Is there any correlation between cortical dysrhythmia and tortuosity of the capillaries?

DR. OSCAR RAEDER: In the family with 2 children, did the father, the son and the daughter all have a neurosis?

DR. ALFRED HAUPTMANN: This paper represents only one part of my study. The function of the capillaries must also be investigated. It is more difficult to evaluate the functional changes than the morphologic. However, the morphologic pattern is as important as the functional behavior. Of course, heart disease, or any other disease, may have an influence on the capillaries, and Müller (Müller, O.: Die Kapillaren der menschlichen Körperoberfläche in gesunden und kranken Tagen, Stuttgart, Ferdinand Enke, 1922) has included a number of pictures of capillary patterns, especially in cases of renal disease. The pictures I have shown here concern patients who have no disease other than neurologic disorders. I found the most immature picture in hysterical patients and the greatest number of tortuosities in patients with anxiety neurosis. Age does not change the morphologic character of the capillaries.

To answer Dr. Denny-Brown, I did not observe the nails especially. One of the residents studied the nails, and he was of the opinion that neurotic patients also show abnormalities of the nails.

To answer Dr. Lennox, in only 3 cases have I had the opportunity of seeing the parents and siblings of epileptic patients. In 1 case, a sister and a brother, without having epileptic fits, had a network of the horizontal variety seen in epileptic persons. In the other 2 cases I did not find any abnormality of the capillaries. Three cases, however, do not mean anything. I did not examine any twins, but I should like very much to do so.

In answer to Dr. Raeder, in the family mentioned, the father, the daughter and the son were all extremely neurotic, and all had highly abnormal capillary patterns.

---

## PHILADELPHIA NEUROLOGICAL SOCIETY

GEORGE D. GAMMON, M.D., *Presiding*

*Regular Meeting, Nov. 24, 1944*

**Curious Lesions of the Spinal Cord: Report of Two Cases.** DR. FRANCIS C. GRANT and DR. HENRY SHENKIN.

L. S., a 16 year old boy, noted sixteen months prior to his admission to the neurologic service of the Hospital of the University of Pennsylvania that he was gradually losing power in his left leg. This weakness progressed until his admission to the hospital; in addition, three months before he began to notice weakness in his right leg. At no time had there been any pain or paresthesia. There had never been any difficulty with his sphincters.

The past medical history is of interest in that there had been complete paralysis of both legs of two months' duration at the age of 6 years. The cause was never determined, but the child improved gradually, and up to the time of his present illness he had been completely well. We have a statement from the hospital confirming this record.

Neurologic examination revealed spastic gait, with a tendency to swing the left hip and foot in a hemiplegic manner. The Romberg sign was positive, with a tendency to sway more to the left. The left lower limb was extremely weak and the right moderately weak; both limbs were spastic. All reflexes in the lower limbs were hyperactive; the patellar reflex and the achilles were elicited on both sides. The Babinski sign was present bilaterally. All the abdominal reflexes were absent. There was an indefinite level for pain, touch and temperature sensations at the sixth thoracic dermatome, with sacral sparing. Position and vibration sensations were absent in both lower limbs. The upper limbs and the cranial nerves were entirely normal.

The spinal fluid dynamics were normal except for a partial block in the Queckenstedt test. The total protein was 21 mg. per hundred cubic centimeters.

Plain roentgenograms of the thoracic portion of the spine showed changes in the epiphyses and the bodies of the vertebrae, from the fifth to the twelfth dorsal, commonly associated with Scheurerman's disease. The intervertebral pedicular measurements were normal. A myelogram obtained after cisternal injection of Pantopaque (an iodized poppyseed oil) showed a block at the fifth thoracic interspace. The lesion was suspected of being a spinal extradural cyst, although the typical fusiform spreading of the vertebral pedicles was lacking. The possibility of an intramedullary tumor of the cord was also entertained. In any event, operation was clearly indicated.

A laminectomy was performed on Nov. 4, 1944. A white, shiny, intramedullary lesion, which did not seem to be well demarcated from the cord, was exposed at the level of the fifth thoracic vertebra. An incision was made through the pia parallel to the long axis of the cord; it included possibly a very thin layer of the posterior column, although it was doubtful whether there was much cord substance at this point. When the incision was made, there began to extrude the white, soapy, greasy material characteristic of an epidermoid. The cavity was well opened, and all its contents were carefully removed. A small piece of the capsule was also removed for verification. The cavity seemed to involve most of the left half of the cord. The patient has done well since operation. He voided spontaneously from the first and was up and walking on the twelfth postoperative day.

Microscopic examination of the section of the cyst wall showed a typical band of stratified squamous epithelium resting on a narrow layer of connective tissue. Keratinized epithelial debris was everywhere present. There was no evidence of accessory structures of the skin.

Epidermoid cysts of the spinal canal are rare tumors and apparently arise from misplaced rests of epithelial tissue, probably due to improper separation of neuroectoderm from surface ectoderm. It is interesting to note that this boy had complete paraplegia at the age of 6 years, which underwent complete remission in two months. In view of the congenital nature of the tumor, it is not too much to assume that this paraplegia was related to the lesion removed ten years later.

M. F., a previously healthy, 20 month old child, was first seen at the Children's Hospital on June 18, 1943, with a history of irritability and drowsiness of one week's duration. Examination at that time showed high fever and cutaneous lesions of a papular nature scattered over the arms and legs. The child was admitted to the hospital with a diagnosis of erythema multiforme or septicemia. (Lumbar puncture revealed nothing abnormal except for a total protein content of

250 mg. per hundred cubic centimeters. Three weeks later the tap was repeated, and the total protein then measured only 20 mg. per hundred cubic centimeters. The cutaneous lesions cleared; the child's condition improved; he ate well and became more active. He was discharged on July 7, 1943.

However, ten days later, on July 17, he again became irritable and restless and refused to walk or stand. Examination at this time showed marked ataxia of the lower extremities, exaggerated patellar reflexes and suggestive cervical rigidity. Lumbar puncture revealed clear fluid, a pressure of 85 mm. of water and a cell count of 3 leukocytes per cubic millimeter. The Queckenstedt test showed partial block, and the total protein measured 400 mg. per hundred cubic centimeters.

Eight days after his second admission there developed a persistent ankle clonus and a bilateral Babinski sign. Injection of iodized poppyseed oil into the cisterna revealed a block at the level of the fourth thoracic vertebra.

The child subsequently had complete paraplegia with hyperactive reflexes; ankle clonus and the Babinski sign were present bilaterally. No sensory changes were demonstrable. With the patient under ether-procaine anesthesia, the laminas of the fourth, fifth, sixth and seventh thoracic vertebrae were removed. The laminas of the sixth and seventh vertebrae were removed first. The epidural fat had a greenish orange color, with apparent disappearance of the dura itself in this region. Under the lamina of the fifth thoracic vertebra the end of a mass lesion which seemed to involve the dura was disclosed. The bones of the fourth and fifth thoracic vertebrae were carefully removed; there was complete absence of the epidural fat, and a curious, greenish, soft, fluctuant lesion appeared. The lesion appeared to extend upward just under the lamina of the third thoracic vertebra. The more the lesion was exposed, the greener and more apparently cystic it became. While better exposure was being obtained, in order to make a photograph, it was noticed that the lesion itself was becoming less prominent. The reason was that a brownish, gelatinous, coffee-like material was draining from its upper end. With the escape of this fluid, the cyst collapsed, before a satisfactory color photograph could be obtained. The lesion definitely involved the dura, which was removed with the cystic mass. It seemed to lie between the layers of the dura. Removal of the lesion was complete.

Convalescence was relatively uneventful, and on his discharge, three and one-half weeks after operation, the child was able to walk with assistance. When he was last seen, six months after operation, he was able to walk and run about normally.

The microscopic appearance of the specimen removed at operation was typical of the subdural hematomas occurring in the intracranial cavity. It consisted of a connective tissue membrane, the inner portion of which was a relatively loose meshwork containing many dilated, thin-walled capillaries filled with blood. The outer portion of this membrane was composed of denser fibrous tissue and was limited by a single layer of flattened cells. Blood pigment was scattered throughout the inner portion of the membrane.

A fairly complete survey of the literature failed to reveal any similar case. However, in our own collection, we have 2 cases of epidural bleeding, both in adults, in 1 of which the lesion was definitely related to trauma, without fracture of the vertebrae. In this case, in which operation was performed eighteen hours after the trauma, no membranes were found. In the first case, there was no definite history of trauma, and a hematoma with membrane was observed.

The origin of the hematoma reported here is not clear. There was no history of trauma. It would appear that the bleeding was spontaneous and was related to a systemic, infectious process. The nature of the lesion, however, cannot be doubted, in view of its pathologic appearance and the subsequent full recovery of the child on its removal.

DISCUSSION

DR. HENRY T. WYCIS: I should like to ask Dr. Grant how frequently he thinks such epidermoid tumors occur. Has he encountered any other cases? I recall only 1, that of Dr. Fay, and in this case an epidermoid filled the entire sac.

DR. GEORGE D. GAMMON: I should like to ask whether the preceding paralysis, such as occurred in this case, is commonly associated with epidermoid cysts. My associates and I were puzzled how to explain the paraplegia which the youngster had ten years before his second attack of paraplegia. He was admitted to the Tuberculosis Hospital at Mount Alto, Pa., but apparently no evidence of tuberculosis was found at that time.

DR. B. J. ALPERS: Was there any connection with the meninges in the second case? I do not know of any instance in which a cerebral epidermoid has been intramedullary. There are epidermoids in the skull, and epidermoids of the brain are entirely extramedullary. One of the interesting features of this case is the intramedullary character of the tumor. I wonder whether the tumor was one which had pushed its way into the substance of the cord or whether it was in fact a medullary tumor. I raise this question because epidermoids should arise from extramedullary sources rather than within the brain substance itself.

DR. MICHAEL SCOTT: I should like to ask Dr. Grant whether any thought was given to the possibility of the presence of typical scurvy, vitamin C deficiency or any type of blood dyscrasia in the first case.

DR. FRANCIS C. GRANT: As to our experience with epidermoids of the spinal cord, I can state that this is the only case I have ever seen of a tumor of this type in the spinal cord. I can give no details, therefore, as to the duration of symptoms except in this particular case.

The tumor lay, as far as I could judge, beneath the pia. Certainly, there was a fine, tough membrane over the surface of the tumor which had to be sectioned before intracapsular removal was possible. This membrane may have been the pia, or it may have been the capsule of the tumor. The microscopic sections may throw light on this point.

With regard to the hemorrhagic lesion in the first case, which both from the position at operation and from pathologic evidence seemed to be an intradural blood clot, no evidence of either scurvy or blood dyscrasia was noted, and there was no history of antecedent trauma. In 2 previous cases in our records, in which the bleeding was obviously epidural, there was a history of trauma to the spinal column, and in 1 of them there was, in addition, pronounced hypertension.

**Function of the Anterior Cerebellar Lobe.** DR. GERVASE J. CONNOR.

Within the anterior cerebellar lobe are represented probably all stages of cerebellar development—the archi-

cerebellum, the paleocerebellum and the neocerebellum. In the dog ablation of this region provokes a profound extensor release in the antigravity muscles, of such a character that these muscles become abnormally responsive to extensor postural influences, whether of local, segmental or general static nature. This leads to strongly hyperactive reflexes of stance, incoordination in all the extremities, hyperactive and spreading deep tendon reflexes and well defined lengthening and shortening reactions, or plasticity.

In the single case of a tumor of the anterior cerebellar lobe in man, signs of a similar, but more subtle, nature are observed. It is not so much the local postural responses themselves as their susceptibility to modification from segmental and suprasegmental sources that characterizes this syndrome.

There is evidence to suggest that within the anterior cerebellar lobe there is resident a discrete type of functional localization, so precise that individual extremities and the labyrinths are specifically represented.

DISCUSSION

DR. HENRY T. WYCIS: I should like to ask Dr. Connor two questions: First, what are the probable compensatory mechanisms which account for the waning of the exaggerated postural reactions following ablations of the anterior lobe? Second, what is the influence of bilateral labyrinthectomy on the postural reactions appearing after ablation of the anterior lobe?

DR. HENRY SHENKIN: I have had no experience with this region, but I should like to ask whether Dr. Connor noted any sensory changes in his animals with ablations of the anterior cerebellar lobe. There are some isolated reports by other investigators of sensory changes observed in cerebellar preparations.

DR. GEORGE D. GAMMON: I should like to ask Dr. Connor about the time course of these various phases and what the ultimate condition is. How rapidly do these animals recover? Is the first phase described as the "exaltation" of Luciani?

LIEUT. COMDR. WILLIAM GERMAN (MC), U.S.N.R.: I should like to comment on some of the clinical aspects that Dr. Connor mentioned. The case I shall describe presented the puzzling problem of a patient who appeared to have a cerebellar lesion; yet, because of the positive nature of his ataxia, I was inclined to think that the lesion was a contralateral frontal one. In other words, he did not fall to the side; he pushed himself over to one side. It was just as Dr. Connor described it—an excessive support reaction. His process of standing was a caricature of excessive standing. In fact, he stood so hard on the affected side that he pushed himself over to the other side, and in walking he progressed in the same manner. I have never seen such forced ataxia except with frontal lesions.

The patient had given a history of gradually progressive disability over a long period, with few or no signs of increased intercranial pressure, and it was not until my colleagues and I had made an injection of air that we were quite certain that his lesion was in the left cerebellar region. It turned out to be as Dr. Connor might have predicted had he seen the patient before the operation. The tumor, in the left anterior cerebellar lobe, was of hemangiomatous origin.

After the operation, Dr. Connor reviewed the situation with us and demonstrated the postural tonic changes which occurred in the reflexes and in the extensor rigidity. There was a striking relaxation of extensor tonus in the left lower extremity when the patient's head was turned to the middle or away from the side of the lesion. When his chin was turned to the side of the lesion, a sustained ankle clonus was elicited on the left. Similarly, when the head was turned to the side of the lesion, there was a very active knee jerk on the same side. The extremity would tend to remain in a position of extension and then gradually drop. I have seen no other cases in which these signs were brought out so strikingly, but perhaps it was because I did not know what to look for. One does not see tumors in this location frequently. It would seem that at least part of this picture should be found in cases of tumors of the cerebellopontile angle. Perhaps it is masked by some of the other effects present.

DR. GERVASE J. CONNOR: I do not know whether sensory disturbances were present. Various sensory examinations were carried out, but the results were not sufficiently accurate in the animal to permit a conclusion.

One of the most interesting parts of the study concerned the effects of labyrinthectomy on the anterior cerebellar syndrome. I purposely omitted discussion of this subject in order to avoid confusing the picture. From a functional viewpoint, one should regard the anterior lobe as a crossroads of the vestibular and the spinocerebellar system. These systems exert a conspicuous effect on the postural pattern. When the labyrinths are removed during the early postoperative period after anterior decerebellation, there is lessening of the extreme extensor dominance, but the extensor muscles in the extremities remain abnormally responsive to local and sequential static influences. It would appear that the fundamental physiologic effect in the extremities after removal of the spinocerebellar portion of the anterior lobe is equivalent to the partial deafferentation of these extremities, the stretch reflex arc remaining intact. Removal of the vestibular portion of the anterior lobe would seem to result in a parallel effect on the labyrinths. This concept would be entirely consonant with Sherrington's oft repeated parallel between the labyrinths and the proprioceptive mechanism in the extremities.

It is difficult for me to be as specific as I should like in answer to Dr. Gammon's question. The time course of the various phases is sharply dependent on the completeness of the ablation. Even small residual areas of cortex are important in this connection. I did not emphasize the time relationships of the various phases in the dog because they are of so much less practical significance than is the composite postural picture. The extreme extensor exaltation, similar to that described as the "exaltation" of Luciani, may last for several weeks, depending on one's definition of the term. Its temporal limits are not easily defined because the exaggerated standing is evident as soon as the animal can get to its feet. Thereafter the phases in recovery merge smoothly one into the other. In the monkey, the phase of extreme extensor exaltation is not very conspicuous. In the anterior decerebellate monkey the extensor exaltation does not completely dominate the mechanism for stepping, even though the positive supporting reaction is exaggerated.

The compensatory postural mechanism may well reside in part in the extrapyramidal system in the cerebral cortex. One would expect a certain amount of encephalization of anterior cerebellar function in animals higher than the dog.

## CINCINNATI SOCIETY OF NEUROLOGY AND PSYCHIATRY

ALPHONSE R. VONDERAHE, M.D., *Presiding*

*Regular Meeting, Dec. 18, 1944*

**Studies on Flying Personnel with Operational Fatigue: II. Modification of Pentothal Therapy.** LIEUT. COL. BENJAMIN H. BALSER, Medical Corps, Army of the United States.

Recently a group of patients with operational fatigue were treated at a regional station hospital. Intravenous pentothal therapy was used, and in several instances it was noted that the patients failed to improve with it. A recording device was obtained, and with the patients under the influence of pentothal (in a hypnotic state) their productions were recorded on a radio recorder, a hand microphone being used. While the patients were under pentothal narcosis, they spoke freely and vividly of their emotion-laden experiences in the various theaters of combat. However, on recovering consciousness they remembered little of their production. On the day following the treatment and recording, the patients were brought into the office and their records played back to them. The response was dramatic. They went through a tremendous anxiety reaction, during which they perspired freely, were tearful, showed tremors of the jaw, hands and body, sat with their hands and fingers clenched tightly and were obviously under extreme emotional stress. After this, each patient's illness was discussed with him, and he was given an opportunity to return for further discussions, at his own request.

With this form of treatment, these patients responded quickly, and much more rapidly than they did without the use of this mechanism. Final proof of such recovery was evidenced in the ability of a group of these patients to make humorous records similar to, yet mimicking, the productions that they had made while under pentothal hypnosis.

DISCUSSION

DR. CHARLES D. ARING: This is a provocative contribution to the manifold technics known as psychotherapy. This seems to offer another glimmering of hope that the tedious process of psychotherapy may eventually be shortened, as it must be to prevent collapse under its own weight.

Fully cognizant of the fact that one rarely sees in civilian practice the type of patient described by Major Balser, one wonders, nevertheless, whether certain psychologic disorders in civilian life might not lend themselves to pentothal therapy or its modification. The civilian neurosis is engendered a bit differently than the war neurosis. It is almost always the product of a long series of what are to the patient traumatic episodes. The period of development of the military psychologic disorder is compressed by stimuli that are comparatively tremendous, though they impinge on persons who had undergone a certain selection.

A reasonable solution to the impasse that now exists in handling the countless cases of curable psychologic illness would appear to be the introduction of shortening technics. Possibly the war will render one of its few services by forcing their development more quickly than would otherwise have occurred.

DR. MILTON ROSENBAUM: I predict that the method will not hold up in civilian psychiatric practice unless there has been relatively recently a traumatic precipitating event. Psychiatrists have been using pentothal for the post-traumatic neuroses. I remember particularly one patient, a young man in whom a neurosis had developed after an automobile accident three years before, in which a girl companion was killed. This man was married, with several children. My associates and I discussed this girl with the patient but were able to obtain only the most desultory statements about her. With the use of pentothal we learned that the girl was married and that the patient and she were in love. He had broken off their affair, but she had somehow managed to meet him and during this automobile ride had told him of her love for him and her desire, after their respective divorces, for them to marry. He had the instant thought that he must be rid of her, and the accident followed immediately. With the careful use of this material, obtained with the patient under pentothal therapy, it was possible to rehabilitate him.

Several years ago David Lewy described what he called release therapy. He worked with young children who presented symptoms of anxiety of relatively short duration. Using play technics, he allowed the child to "act out" the situation which had precipitated the acute behavior disorder. In the "acting-out" process there was a good deal of emotional release. However, this method was helpful only in those cases in which there had been a relatively recent traumatic event. In cases of the more chronic type intensive psychotherapy was needed.

I think that some of the problems in the treatment of acute battle neurosis and civilian neurosis are indicated by Lewy's work. When a neurosis is precipitated by a recent and intense traumatic event which is then suppressed, use of pentothal is indicated. However, the usual civilian neurosis has no such dramatic start; indeed, the precipitating event is usually so well hidden that it is overlooked, and the etiologic factors have been operating over a long period.

DR. ALPHONSE R. VONDERAHE: May any one have operational fatigue?

MAJOR BENJAMIN H. BALSER, Medical Corps, Army of the United States: It is probable that any one may have operational fatigue. Capt. David Wright has published some observations on this matter. In a study of a group of 150 men who had finished their tour of duty without obvious psychologic disorder, he found that about 95 per cent had symptoms of operational fatigue, which in about a third of them were severe.

DR. HOWARD D. MCINTYRE: How long will the patients talk when under pentothal narcosis?

MAJOR BENJAMIN H. BALSER, Medical Corps, Army of the United States: As long as one will permit. One usually allows a period of ventilation and then ends it by saying, "All right; that's enough. Now you can go to sleep." The patient will sleep about fifteen or twenty minutes and then be up and around.

With the patients who had not responded to ordinary pentothal therapy and to whom the voice records were played back, I usually waited three to five minutes after the record had finished to begin my talk. Only one session was required. I did not know what I was going to meet. Psychotherapy was on a most superficial level. I talked softly and explained to the patient that he was completely normal before the grafting of this illness on his normal personality and that the illness was as he described it himself in the phonograph record. With these 12 patients only one phonograph recording was required to effect an apparent recovery. The men were then transferred to a rest camp, and I do not know their adjustment thereafter.

In ordinary pentothal therapy the first session may require administration of more of the drug than subse-

quent ones, and more stimulating words may be necessary to start the patient talking. A trigger word may be the name of a city which was the goal of a bombing expedition, or it may be the wife's name. These stimuli start talk, and it usually continues until the therapeutist terminates the interview.

During the injection of pentothal, which is done slowly, the patient is asked to count backward from 100. When he begins to mix figures, the end point is reached. This phenomenon is usually followed by nystagmus and then by pseudobulbar speech.

My associates and I have had no improvement with continuous narcosis, contrary to the reports from England. This may be due to the factor of the delay in these patients reaching us.

CAPT. JOSEPH LANDER, Medical Corps, Army of the United States: Col. Roy Grinker has a unique setup in Florida, where most of the patients have rather severe combat fatigue. The rate of return of fliers to combat flying is not high, though many are restored to other types of duty.

Grinker stresses the use of the "twilight state" as the patient emerges from pentothal narcosis for the giving of much reassurance and treatment; impressions gained by the patient at this time are of considerable effect.

It is the feeling of some workers that if one were to spend hours with the patient one could achieve about as much as one does with pentothal, but pentothal therapy is a short cut. There are advantages and disadvantages to the use of such a short cut. It saves a great deal of time and produces prompt results. On the other hand, the elimination of a cooperative ego means that the therapeutic result is likely to be less lasting than it would if the total personality participated in the treatment. When one has the "whole personality" working with one, the cathartic and insight values are assimilated far more thoroughly.

However, the primary concern of the Army is a quick and wholesale rehabilitation; for this reason, among others, pentothal treatment is an extremely valuable procedure.

Another point to be borne in mind is that treatment on the spot, a few days after the onset of the disturbance, is likely to be far more effective than that administered months, and sometimes a year, after the syndrome has appeared and become relatively fixed. For this reason, I expect that the results of pentothal treatment overseas will be far more encouraging than here.

DR. I. MARK SCHEINKER: I wonder whether the beneficial and prompt results obtained with the method developed by Major Balser would not warrant the drawing of a certain parallelism with those results Freud obtained in his early period of psychotherapy. In his protocols, Freud described the immediate dramatic effect obtained in a series of cases through a hypnotically induced "revival" of the psychogenic trauma.

# Book Reviews

**The Basis of Clinical Neurology.** By Samuel Brock, M.D. Second Edition. Price, $5.50. Pp. 393, with 72 illustrations. Baltimore: Williams and Wilkins Company, 1945.

It is hard to believe that the first edition of Dr. Brock's book was as recent as 1937 in view of its wide acceptance and of the numerous generations of medical students brought up in its tradition. One is not surprised to learn from the present edition that the text has been translated into Portuguese, for it is truly a one volume encyclopedia of applied neuroanatomy and neurophysiology.

It is an axiom that in a work of this kind there are many subjects which cannot receive full consideration; emphasis must be the more or less arbitrary prerogative of the author. While a section on electroencephalography has been added by Dr. Paul F. A. Hoefer, the rising importance of this technic in present day neurology would merit more space. A section by Dr. Joseph Moldaver on electrodiagnostic methods is included, and Dr. Irving Simons has revised the section on urination.

The book is of sufficiently excellent quality that the reviewer may freely make suggestions without impugning its essential value. Especially could one wish for an amplification of the index, which is much too brief. In addition, the bibliography is awkwardly arranged. Divided as the list is into sections which follow groups of allied chapters, one is forced to leaf back and forth for the necessary connections. It would be much better to have the complete bibliography at the end. Furthermore, the additional use of fine print would increase the readability of the text; too much detail in the body spoils it for rapid review, and the style is rather pedestrian.

Dr. Brock's book, in its first edition, won its place. The second edition continues to be indispensable.

# News and Comment

## ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASES

The trustees of the Association for Research in Nervous and Mental Diseases have voted to postpone the next meeting of the association, usually held in December, for a year. The subject for discussion will be "Epilepsy."

Archives of Neurology and Psychiatry

VOLUME 54 OCTOBER 1945 NUMBER 4



# ACUTE WAR NEUROSIS

## SPECIAL REFERENCE TO PAVLOV'S EXPERIMENTAL OBSERVATIONS AND THE MECHANISM OF ABREACTION

WILLIAM SARGANT, M.B. (CANTAB.), M.R.C.P., D.P.M., AND
H. J. SHORVON, M.B., D.P.M., D.A.
LONDON, ENGLAND

Since the beginning of the war many psychiatrists and neurologists have referred to the importance of "conditioning," in the Pavlovian sense, in the origin and perpetuation of acute war neurosis. Sargant and Slater [1] (1940), reporting on the acute neurotic casualties from Dunkerque, suggested that a process resembling "conditioning" was seen in these patients in a simple form and that the success of physical methods of treatment indicated that physiologic processes played a considerable part in the development of an acute neurosis. Love,[2] in 1942, emphasized the usefulness of a Pavlovian approach to the problems of acute war neurosis, as he had experienced them in the campaigns of the Middle East, and especially during the siege of Tobruk. Symonds,[3] in a recent paper on the human response to flying stress, used Pavlov's [4] observations to discuss methods of inhibition of fear. Methods of "deconditioning" recently acquired fear responses have been the subject of many experiments in World War II. The beneficial effects of emotional abreaction in the acute battle casualty from the intravenous use of barbiturates were also described in the paper by Sargant and Slater [1]; and one of the purposes of the present article is to relate this short-cut psychotherapeutic procedure, developed by Horsley in peacetime, to Pavlovian concepts and to other methods of physical treatment.

In our unit at Sutton Emergency Hospital and elsewhere, we, together with our associates, have treated some 10,000 neurotic casualties, drawn mainly from the services. These patients have included, besides those from Dunkerque, who have already been referred to, casualties from the Battle of Britain and the London blitz, patients from the Mediterranean battlefields and a considerable number also from the battlefields of Normandy. Throughout this period we continued to see neurotic reactions to stress which could be discussed on a basis of Pavlovian conditioning. At the beginning of the fighting in Normandy, Major Howard Fabing, Medical Corps, Army of the United States, suggested to one of us (W. S.) that we try to reexamine these patients in the light of Pavlov's recently translated work "Conditioned Reflexes and Psychiatry." [5] This we have done, and we have also made use of Professor Frolov's [6] book "Pavlov and His School." We have learned much from many conversations with Major Fabing, and some of his ideas must have become inextricably interwoven with ours. We take responsibility for them, however, in their present form, particularly for what we have to say on the subject of ether or amytal abreaction. Some of our observations seem worthy of discussion, since they throw light on the problem of etiology and treatment of neuroses in general and of therapeutic abreaction in particular. But it must be stressed that any theories put forward are tentative and are intended principally to stimulate further research.

### PAVLOV'S CONCEPTS

Pavlov visualized the cerebral cortex as a vast, intricate and integrated structure, constantly receiving excitatory and inhibitory stimuli, both from the outside world and from the internal medium. These stimuli have definite areas of reception in the cortex, in which complex conditioned (temporary) reflexes are elaborated and conducted along special paths. The conditioned

From the Sutton Emergency Hospital Neuropsychiatric Unit (Maudsley Hospital, London).

1. Sargant, W., and Slater, E.: Lancet **2**:1, 1940.
2. Love, H. R.: M. J. Australia **2**:137, 1942.
3. Symonds, C. P.: Brit. M. J. **2**:740, 1943.
4. Pavlov, I. P.: Lectures on Conditioned Reflexes: The Higher Nervous Activity (Behaviour) of Animals, London, Lawrence & Wishart, 1928, vol. 1.
5. Pavlov, I. P.: Lectures on Conditioned Reflexes: Conditioned Reflexes and Psychiatry, London, Lawrence & Wishart, 1941, vol. 2.
6. Frolov, Y. P.: Pavlov and His School, translated by C. P. Dutt, London, Kegan Paul, Trench, Trubner & Co., Ltd., 1938.

reflex is distinguished from the unconditioned reflex (or stimulus, or instinct), which is constant and inherent, with an anatomic center in the subcortex or the basal ganglia. The unconditioned reflexes are concerned with food, defense, sex and other fundamental drives. They are the basis for individual adaptation, are essential for the preservation of the species but act only in limited situations and are obviously insufficient for higher adaptation. Finer adjustment, the equivalent of learning from experience, is made by means of the conditioned reflexes. The cortex analyzes and synthesizes external and internal stimuli and regulates the activity of the basal ganglia. In addition to the subcortical and cortical systems, which have arisen in the course of evolution, there is, according to Pavlov, in the human brain a special third system located primarily in the frontal region, which subserves abstraction and speech. Pavlov called the conditioned stimuli of the conditioned reflexes "signals"; and he regarded words as the "equal of signals," or "the second signaling system." This most recently developed function of the human nervous system is also the one most easily disturbed in mental disorder.

Pavlov formulated a series of physiologic laws governing the phenomena of excitation and inhibition—their irradiation, concentration and mutual or reciprocal induction. In a normal personality they show a well balanced equilibrium, within limits. Beyond a certain limit of strength, a stimulus produces not an increased but a decreased effect. When the limit of stimulation has been exceeded, a temporary inhibition follows. During this period, which is accordingly known as the "equivalent," or "paradoxic," phase, a strong stimulus produces a response which is only equal to, or is even smaller than, the response excited by a weak stimulus. The level of stimulation at which this effect occurs is determined, among other things, by the constitutional makeup of the experimental subject.

Pavlov was led by his work on experimental neuroses to classify the types of nervous systems of his dogs in much the same way as Hippocrates classified the temperaments of man. He recognized those in which excitation predominated (the choleric and the sanguine, the excitable and the lively) and those in which inhibition predominated (the phlegmatic and the melancholic, the calm and the inhibitory). The sanguine and phlegmatic types form a central group, of greater stability than the others. Pavlov expressed the belief that a morbid state could be brought about by very strong stimulation, either excitatory or inhibitory, or by the "collision" of excitatory and inhibitory processes. The direction in which breakdown occurs depends on the form of the stress and on the type of the nervous system. By these means he tried to explain the symptoms of neuroses in man, such as hysteria, obsessional states and paranoid ideas. In hysteria there is a predominance of inhibition; the cortical cells become incapable of work as a result of stimuli which would not affect the activity of the normal cortex. The inhibition is thought to be protective, and, depending on its extent, intensity and depth, one sees the phenomena of sleep (widespread irradiation), hypnosis (partial irradiation) and hysteria. The concept of the "weak," "inhibitory" nervous system may be interpreted by the psychiatrist to denote the constitutional weakness of the neurotic person.

The phenomena of the "equivalent," "paradoxic" and "ultraparadoxic" phases, as they have been described by Pavlov in animals, are of particular significance in the present discussion. We have frequently observed somewhat similar forms of behavior among battle casualties. The equivalent and paradoxic phases have already been mentioned. Under still more intensive stimulation, excitatory conditioned stimuli may come to have an inhibitory effect, and vice versa; this is the ultraparadoxic phase. In Pavlov's terminology, such stimuli are called "transmarginal," and the inhibition produced is called "ultraboundary inhibition." In this state the cortical cells become for a time incapable of work, and the animal enters a condition resembling stupor. Excessive stimulation is required to produce this state in the normal cortex, but the threshold is lower in dogs with a weak, inhibitory type of nervous system. Once produced, ultraboundary inhibition may quickly spread over the whole cortex and stop its activity.

A striking example of the ultraparadoxic phase, with the production of ultraboundary inhibition and what Pavlov called "rupture" of the higher nervous activity, was provided by the Leningrad floods of September 1924. These floods penetrated Pavlov's laboratories and subjected his dogs to a terrifying experience. The dogs were in low cells with exit doors close to the floors. Before they could be rescued, the cells were nearly full of water and the dogs could barely keep their heads above water. To get them out of the low exit doors, they had to be dragged under water. After this experience, all recently acquired conditioned reflexes were found to have been abolished in some of the dogs, and it was months before they could be restored. Even thereafter they could be abolished again by any stimulus similar to that of the flood ex-

perience, for instance by a trickle of water running under the door of the cage. According to the Pavlovian theory, the intense excitement caused by the flood had brought about in succession the ultraparadoxic phase, ultraboundary inhibition, rupture of higher nervous activity and abolition of recently elaborated patterns of conditioned behavior.

### COMPARISON OF PAVLOV'S EXPERIMENTAL RESULTS AND CLINICAL OBSERVATIONS

Among the patients who came direct to us from the Normandy battlefields, there were, aside from those who showed the usual anxious and depressive symptoms, men with states of simple but profound exhaustion; others with gross, incoordinated, irregular jerking and writhing movements of the limbs and trunk, often accompanied with aphonia or stammer or explosive speech, and yet others in various states of stupor. It was in these patients with hysterical reactions that parallels to Pavlov's experimental observations could most frequently be seen, not only during their period of observation in the hospital but in their behavior of the past as preserved in the field records.

The human nervous system is normally in a state of dynamic equilibrium. But when it is subjected to excessive stimulation, it may pass into a state in which excitation or inhibition predominates and it is incapable of intelligent work. Instances have been reported in which soldiers have broken down into intense excitatory states while in the line, have run at random across no man's land or dashed blindly into machine gun fire. One of our patients advanced twice to help a friend whose leg was blown off but could not bring himself to do it. He then passed into a state of excitement, in which he banged his head repeatedly against a tree and then rushed about wildly, calling for an ambulance. On its eventual arrival, he had himself forcibly strapped down. Another man, after his friend had been killed, tried to rush out to tackle a German tank single-handed; he had to be held down by his comrades and dispatched to a psychiatric center. In these examples, beyond the general state of excitation, there seems to be an inhibition of normal judgment.

States of inhibition appearing in similar circumstances are exemplified by men who passed into a state of stupor or exhibited amnesias or fainting attacks. There were patients who were literally paralyzed with fear. Others passed into states of simple exhaustion; they were usually men of fairly stable personality who had experienced, in addition to mental stress, deprivation of food and sleep. In some cases inhibition seemed to be limited to a smaller area. One patient, for instance, only stammered when there was talk of an officer who had reproved him for cowardice. Loss of voice, followed during recovery by stammering, was common. This frequent disturbance of the "second signaling system" may be due, as Pavlov suggested, to its recent evolutionary development and consequent liability to disturbance by excessive or ultramaximal stimulation. Other forms of focal inhibition were shown by men with a rigid facies, the feeling of a lump in the throat, or a bent back and "weak legs" but without paralysis of the lower limbs. Paralysis of the legs was uncommon, though the gait was often slow. Pavlov described a similar progressive inhibition in his animals submitted to a bombardment of stimuli, starting in the region of the mouth and forward parts of the body and only finally extending to the hindlimbs.

As a rule, there were both focal excitation and focal inhibition. Some patients showed rigidity or inhibition of facial movements or speech combined with tremor or excitation of the hands. Or paralysis of speech might be combined with jerking of the neck. Acute anxiety was often accompanied with inability to swallow. The upper part of the body might shake violently while the lower part was still. A passive or laughing face might be combined with tremors and distorted jerking and writhing movements of the limbs and body.

In these patients with mixed excitation and inhibition, there had been not infrequently sudden changes from one state to the other. One man had been lying trembling in a ditch and feeling paralyzed with fear when his company was about to attack. His officer taunted him with some such remark as "a girl would put up a better show." The man suddenly became wildly excited, shouted to his comrades "Come on, boys!" leaped out of the trench to the attack and "passed out." Other men became panicked and ran about screaming, this phase being followed by sudden total loss of voice. One of our patients collapsed and lay paralyzed and speechless in a village street that was being bombed at the time; but he started suddenly to scream and struggle when he was picked up by his comrades. It is important to note that in a great deal of the abnormal behavior that was observed among these men no motive of gain could be discerned.

These sudden states of total inhibition or collapse which are seen after stress may be examples of Pavlov's ultraparadoxic phase, in which widespread inhibition abolishes normal conditioned

reflexes. Conditions analogous to ultraboundary inhibition were encountered by us, for example, in men who arrived at the hospital in a complete hysterical stupor. Similar states were later induced artificially by stimulation of the patient under ether.

These abnormal states may develop into what Pavlov has termed a dynamic stereotypy, that is, a functional system in the cortex which requires less and less nervous work to maintain it. The repetitive pattern of movements and jerks shown by some of our patients did not yield rapidly to ordinary methods of treatment, such as removal to a hospital and rest, and strong and new stimuli had to be applied to break up the pattern. However, with excessive stimulation under ether, as described later, the condition might rapidly pass off. The stereotypy was not found to be clinically a constant and exactly repetitive pattern, any more than it was in Pavlov's experiments; it was "chaotic" and tended to fluctuate in an irregular fashion.

Somewhat more difficult to describe in terms of Pavlov's theories was a small group of patients whom we saw in our Normandy material. These were men who showed an acute schizophrenic-like syndrome, which we believe on clinical grounds to be an unusual hysterical reaction. Hubert [7] has given a clinical description of similar states which he observed near the front line in the Battle of France. In Pavlov's terminology, this syndrome might be regarded as resulting from an oncoming general inhibition of the cortex, thereby releasing the neighboring subcortex from control; by the mechanism of positive induction there might then ensue a chaotic excitation of the cortex, producing the hallucinations and delusions which are features of this state. These patients usually rapidly responded to deep sedation, which would protect the cortex from subcortical stimulation.

### RESPONSE TO TREATMENT

Pavlov's observations may also be related to the results of treatment. He found that under appropriate handling dogs with a "strong," "excitatory" type of nervous system were less liable than the "weak," "inhibitory" type to the development of neurotic states; once a neurosis had been built up, they were, moreover, more likely to respond to early treatment with large doses of bromides. We also have found that men of more stable types of personality are less likely to suffer neurotic states, that when these states occur they are relatively more often exhaustive syndromes and that these men respond frequently to treatment with rather short periods of rest and heavy "first aid" sedation (Sargant [8]).

Among the patients who came to us from Normandy, some had already had three to seven days' treatment with continuous narcosis at advanced psychiatric centers in France; they were evacuated to England when response to treatment was unsatisfactory. Others of the men we received had had only treatment at field dressing stations and were sent to England direct, owing to overcrowding of the psychiatric units in France. The former group were much more heavily loaded with family histories of psychosis or neurosis, and many more of them had had previous nervous breakdowns and had already been seen by army psychiatrists before D day. They could be classified as being of the "weak," "inhibitory" type, and, as Pavlov might have predicted, hysterical reactions predominated.

The physical methods of therapy used by us have been reported in previous articles from this unit. They were continuous narcosis (Sargant and Slater [1]), modified insulin therapy (Sargant and Craske [9]) and combined insulin and narcosis treatment (Sands [10]). Many of these men had remained at duty for some time after the onset of symptoms and had suffered physical deterioration. Losses of weight up to 25 pounds (11.3 Kg.) were recorded. It is perhaps interesting that Pavlov himself commented on the fact that such factors as loss of weight, infections and endocrine disturbances diminished the stability of conditioned responses. We found that patients with stupor and hysterical states of the inhibitory type did best with some form of abreaction before sleep treatment was engaged in. Patients with generalized excitation did well when given sleep treatment immediately. After sleep treatment, both groups of patients went on to receive insulin treatment in order to stabilize recovery and restore weight.

The history of abreaction is a long one. In World War I it was often used with the patient under hypnosis. In World War II the technic of abreaction with barbiturates has been more frequently employed, and this was our usual method until the time of the Normandy campaign. The method does not now require description. A technic of abreaction with ether was developed by Palmer in North Africa, in 1942. As we used it, it may be briefly described as follows: The patient is put into a relaxed state, and a preliminary discussion of events before his break-

7. Hubert, W. H. de B.: Lancet **1**:306, 1941.

8. Sargant, W.: Brit. M. J. **2**:577, 1942.

9. Sargant, W., and Craske, N.: Lancet **2**:212, 1941.

10. Sands, D.: Brit. M. J. **1**:763, 1944.

down is begun. He is then encouraged, under light etherization with an open mask, to put himself back in the situation where his breakdown occurred, or in any situation in which events of strong emotional significance took place, such as being subjected to mortar fire, shelling or bombing. If this is done successfully, the man usually becomes quickly and wildly excited and starts to abreact. The voice becomes louder; the face reddens, and the flush becomes deeper as the emotional release occurs. Some patients became so excited that they had to be held down by one or more doctors.

The intensity of the excitement brought about is generally greater with ether than with amytal, and when the emotional release occurs it is more stormy. Much depends on the way in which the physician handles the situation. With ether the recital of events is more dramatic, and the man behaves as though those same events were happening now. The patient is of set purpose encouraged to cry, to shout and to struggle, as the greater the degree of excitement the better will be the eventual therapeutic results. This artificially induced state of excitement appears to break through localized foci of inhibition and thereby restore a lost memory, bring back speech where there has been aphonia or replace a stammer with normal articulation: we have seen it break through a massive inhibitory state of stupor.

A point of particular interest is that it was not always essential to go over the whole story to get a successful result. It was the high degree of excitement that was desirable, and for this it might be sufficient to bring the etherized patient back in imagination to Normandy and then to say loudly and firmly, "The mortars are coming over again," and "Look, there's a tank coming down the road!"

Some of the best results obtained with ether were in the abolition of a dynamic stereotypy of thought or behavior. Men with localized hysterical jerkings or a persistent anxious rumination about battle experiences did particularly well when the intensity of artificially induced excitement was so great that at its culmination the patient appeared to "collapse" and go into a state of total inhibition for a short time. This was the condition which seemed to us to resemble the ultraparadoxic phase reported by Pavlov in his animals. These stereotypies of behavior, which differ from other hysterical patterns in which the excitatory process is abnormally "labile," showed an abnormal "inertia"; the excitatory process persisted obstinately despite such treatment as continuous sleep, which might have been expected to alter the excitatory process to an inhibitory one. One might say that the ultraparadoxic phase caused a "rupture" of the stereotyped functional system and that recently built-up conditioned behavior was extinguished in a manner similar to the abolition of the conditioned reflexes in Pavlov's dogs after the Leningrad floods.

In some patients we found that when ether abreaction without the appearance of the ultraparadoxic phase had produced little benefit a satisfactory result was obtained when this phase was induced at a second, and later, attempt. Some patients, however, passed readily into this state with a comparatively mild degree of excitement, went through it perhaps repeatedly and did not do well. They showed as a rule severe hysterical reactions and, according to their past histories, pronounced constitutional instability.

It is important to note that ether abreaction did not produce improvement in all types of patients. An already excited patient, without stereotypy or focus of inhibition requiring abolition, might be made worse by the added artificial excitement. Agitated and intensely anxious patients responded better to simple sedation or to abreaction under amytal, in which excitement is damped down as it is released. With patients like these we found it better to begin with a period of sleep treatment and to try abreaction later if required for a residual symptom. Furthermore, if a patient tended to get so excited as to be unmanageable or to pass from excitement into a state of generalized inhibition all too readily, we found it useful to inject sodium amytal intravenously before beginning the etherization. Finally, it was often found difficult to relieve depressed patients by abreaction, although if an emotional storm was successfully induced improvement often resulted. Grinker and Spiegel [11] have recorded a similar lack of success with abreaction under pentothal in patients with hysterical syndromes in which there was a large element of depression. They noted, however, that a few fits induced with metrazol restored the memory and broke up hitherto resistant patterns of neurotic behavior. We, too, have seen a dynamic stereotypy, not responding during continuous narcosis, clear up immediately after a fit induced at the end of the treatment by withdrawal of barbiturates. Psychoanalysts have suggested that therapeutic convulsions are a form of abreaction. Speculation suggests that this view might be correct, that

11. Grinker, R., and Spiegel, J.: War Neuroses in North Africa: The Tunisian Campaign (Jan.-May 1943), New York, Josiah Macy Jr. Foundation, 1943.

the convulsion represents a violent artificially induced excitation, which is followed by ultra-boundary inhibition, and that the resulting improvement is due to the "rupture" of a recently acquired conditioned pattern of behavior or thought. A similar speculation could well apply to the phenomena of excitation in the early hypoglycemic stage of insulin shock treatment, when the patient may violently abreact, followed by the temporary phase of total cortical inhibition in the deep coma stage. The beneficial effects obtained with use of the faradic brush in treatment of hysterical syndromes during World War I might also be owed to the intensity of this nonspecific form of excitation.

Caution has to be exercised with these methods of treatment, both in the selection of patients and in the after-care. Some men were not always able to bear without help thought content with a strongly depressive tone which had been brought to the surface by abreaction, and they needed additional psychotherapy and sedation. Men of aggressive personality released under the ether much latent aggression, which could not always be controlled for some time afterward. Violent fluctuations in behavior occurred. A previously inhibited patient might become aggressive and abusive for several hours, until some part of the previous inhibition had been restored. A combination of methods of treatment was frequently necessary.

## COMMENT

From the clinical point of view, our most striking observation was the frequency with which we encountered, among some patients with acute neurotic states from the battlefields in Normandy, the series of events represented by the sequence: traumatic experience; abnormal psychiatric state exhibiting stereotypy of behavior or thought; artificially induced state of excitement; sudden collapse of the patient into a condition of total cortical inhibition, and recovery to a more normal psychiatric state. The last three items of this series are in general parlance covered by the term "abreaction." The use of this term dates from the publication of the original paper by Breuer and Freud, in 1895. The use of this process for therapeutic purposes was frequent during World War I, and clinical descriptions reported at the time often end with some such phrase as, "The patient suddenly lay absolutely still," after which comes the statement that the symptom, usually also a form of stereotypy, disappeared. Brown [12] (1920) described the case of a man in whom a tremor of the right hand had developed in battle and who had maintained both the tremor and amnesia for the precipitating incident through two years of treatment, in various military hospitals. During abreaction under light hypnosis he passed into a violent emotional storm, and then "he suddenly lay absolutely still." On recovery from this state, the tremor was no longer in evidence, to the amazement of the patient himself.

For centuries before its psychiatric application, the same method of treatment seems to have been used by evangelists engaged in religious conversion, with the purpose of obtaining an alteration in behavior on the part of their converts. Thus we read in John Wesley's "Journal" [13] for Monday, April 30, 1739:

> We understood that many were offended at the cries of those on whom the power of God came; among whom was a physician, who was much afraid that there might be fraud or imposture in the case. Today one whom he had known many years was the first who broke "into strong cries and tears." He could hardly believe his own eyes and ears. He went and stood close to her, and observed every symptom, till great drops of sweat ran down her face and all her bones shook. He then knew not what to think, being clearly convinced it was not fraud nor yet any natural disorder. But when both her soul and body were healed in a moment, he acknowledged the finger of God.

Grinker and Spiegel, describing the phenomena of abreaction under the barbiturate pentothal sodium, observed in the North African campaign of 1942, reported:

> The terror exhibited . . . is electrifying to watch. The body becomes increasingly tense and rigid; the eyes widen and the pupils dilate, while the skin becomes covered with a fine perspiration. The hands move convulsively, . . . Breathing becomes incredibly rapid or shallow. The intensity of the emotion sometimes becomes more than they can bear; and frequently at the height of the reaction, there is a collapse and the patient falls back in the bed and remains quiet for a few minutes, . . .[11]

Wesley, on Friday, June 22, 1739, wrote:

> While I was speaking one before me dropped down as dead, and presently a second and a third. Five others sunk down in half an hour, most of whom were in violent agonies.[13]

Grinker and Spiegel, describing their results, stated:

> . . . The stuporous becomes alert, the mute can talk, the deaf can hear, the paralyzed can move, and the terror-stricken psychotics become well organized individuals.[11]

Wesley, describing his experience, stated:

> I will show you him that was a lion till then, and is now a lamb; him that was a drunkard, and is now exemplarily sober; the whoremonger that was, who now abhors the very garment spotted by the flesh.[13]

These parallels suggest that phenomena which have something in common have been seen under

12. Brown, W.: Brit. M. J. **1**:142, 1920.

13. Wesley, J.: The Journal of John Wesley, standard edition, edited by N. Curnock, London, Charles H. Kelly, 1909-1916, vol. 2.

a variety of conditions and in a variety of persons but have been brought into relation with quite different philosophic theories. By psychiatrists these phenomena have been produced in individual patients, subjected for the most part to what were taken to be specific psychogenic stimuli. The excitatory and inhibitory phenomena, described by Wesley, among others, as occurring during religious conversion, were obtained by subjecting groups of persons to stimuli of a nonspecific, fear-provoking kind. In their several interpretations, the hand of God has been seen by the religious; the heightening of the transference situation and the release of repressed emotion, by the psychoanalyst; the freeing of the ego, by Grinker and Spiegel. Henderson and Gillespie[14] summarized their views of "narcoanalysis" (Horsley[15]) in the words,

"It is extremely likely that what really is effective in this situation is the doctor's confidence in the treatment." It seems to us that all these interpretations are to some extent inadequate and that one gains in understanding by a consideration in terms of Pavlov's teaching. In these terms the interpretation is purely mechanistic: Excessive stimulation leads to ultraboundary inhibition, a rupture of higher nervous activity and the extinction of recently acquired conditioned reflexes. A point in favor of this view, and against current conceptions of the nature of abreaction, is the observation which has been made both by us and by others, that it is not always necessary to recall to the patient's imagination the precise situation in which the original breakdown occurred; the imaginative recreation of stimuli of a much more general kind may be sufficient.

Pavlov's theories have been disputed by many, but few have disputed the accuracy or reliability of his experimental observations. These observations are, we believe, of great relevance to the problem of formation of neuroses in man. In this paper we have been principally concerned to report, in our turn, our clinical observations. We hope, however, that consideration of both kinds of experiential data in relation to one another may help psychiatrists to take another step in the direction of the comprehensive theoretic synthesis that will one day be attained.

## REPORT OF CASES

We give 7 short case records to illustrate some of the more important observations discussed in this paper, especially with respect to our experiments on the mechanism of abreaction. It must be emphasized that these cases are chosen to demonstrate certain points but should be considered in relation to our more general observations. Failure to produce similar improvement in other types of cases is reported in our paper. The occurrence of the improvements recorded does not mean that the patients were necessarily fit to resume front line duties—some went back to lighter duties, and others were eventually discharged from the army to prevent recurrence of the condition. Many of these patients had further insulin therapy, sedation or psychotherapy to stabilize the improvement obtained.

CASE 1.—This case shows the differing effects of sodium amytal and ether in producing excitation during abreaction and the variable results obtained.

Private R. S., aged 26, according to the medical notes from Normandy, was admitted to the Thirty-Second Psychiatric Hospital crying, unable to speak and paralyzed. A psychiatric history, obtained later, showed that his father drank to excess and that his mother was high-strung. The patient was of the nervous, artistic type. He had won a scholarship to an art school when he was 13 and in civilian life had worked as a skilled painter of china. At the age of 19 he had a nervous breakdown, lasting a few weeks, during which he became depressed and unable to face people. He had spent four and a half years in the army as a driver without reporting sick with nerves. In Normandy he had been taken off driving and put into the front line, and the mortar fire and shelling there produced a rapid breakdown. He did not respond to a fortnight's sedation in France and had to be evacuated. On his admission to our hospital, he was still very retarded and apprehensive. He was placed immediately under sleep treatment because he was so upset. After a week, this was followed by modified insulin treatment. But he remained very tense and anxious. He walked slowly, with bent back and rigid facies. An adequate history was still difficult to obtain because of his apprehension and retardation.

At this stage he was given sodium amytal intravenously. Under the effect of the drug he became freer and described being in a static line under mortar fire for eight days. Then he had to take part in an attack in a wood after crossing a river. In the wood he became increasingly nervous and started to shake. When mortars killed several men near him, he lost his voice, burst into tears and became semiparalyzed. Eventually two wounded men had to take him back to an ambulance. "I felt sort of stunned. I lay down crying. I could not speak, but I could cry and utter sounds." Little emotion could be stirred up by this recital, and there was no change in his condition afterward or the next morning.

He was subjected to abreaction with ether on the following afternoon. The same episode was gone over again. This time the recital was accompanied with far greater emotion and excitement. Finally he became

14. Henderson, D. K., and Gillespie, R. D.: Text-Book of Psychiatry, ed. 6, London, Oxford University Press, 1944.

15. Horsley, J. S.: Lancet **1**:55, 1936. Narco-Analysis: A New Technique in Short-Cut Psychotherapy: A Comparison with Other Methods, London, Oxford University Press, 1943.

so excited that he became temporarily confused, tried to tear off the ether mask and overbreathed in a panicky way until the abreaction was stopped. When he got off the couch, an obvious change had occurred. He smiled for the first time and looked relieved. Three days later he said that his symptoms had largely cleared up after the ether abreaction. A week later he still said, "I am a different fellow. I feel fine." A fortnight later there was no return of these symptoms.

Cases 2 and 3 illustrate the breaking up of the symptoms of a "stereotypy" when excitation induced under ether is carried on to the stage of ultraboundary inhibition. In case 2 it will be seen that when excitation under ether was not carried on to the point at which the patient "collapsed" it failed in its purpose. A second ether abreaction, carried on to the ultraparadoxic phase, was successful in the same patient.

CASE 2.—Private L. S., aged 30, was in a confused and tremulous state on admission to the Thirty-Second Psychiatric Hospital. His history showed that he had always been nervous and was especially so during the London blitz. Generally speaking, however, he had been a happy, jolly person before his breakdown in Normandy. He had spent four and a half years in the army as a driver-mechanic and landed in Normandy on D + 17 day. He was in action several weeks, and his symptoms came on gradually. He was given a week's continuous sleep in France but did not respond to this treatment and had to be evacuated. When we saw him, he was depressed and apathetic. He complained of feeling dizzy and being unable to stand the noise of gunfire or airplanes. His thoughts were focused on his friends who had been killed in France. He could not get them off his mind. The scene that bothered him was a horrible one. One of his comrades had a hole blown in his head and died; another had his chin blown off, and a third had blood spurting from his hand.

He was first treated with sedation and modified insulin treatment, but after a fortnight he complained that he felt worse than on admission. He still could not get the scene in which his friends had been killed and injured out of his mind. The first ether abreaction was now carried out. He was taken over the scene that was bothering him, with considerable release of emotion. He said that he thought that his own head was going to be blown off. No ultraparadoxic phase occurred during this abreaction. When he regained consciousness, he cried and said he felt no better. He could "still see it all in his mind."

A second ether abreaction was given at the same session. This time an exciting incident prior to the one he was worrying about was chosen to restimulate excitement. He had been subjected to mortar fire and dive bombing in a churchyard, and it was suggested to him under ether that he was back in that situation. The patient started clawing at the couch, believing he was in a ditch. He was deliberately stimulated by the therapeutist until he passed into a crescendo of fear and excitement. Suddenly he lay dead still. The ultraparadoxic phase had been obtained. On regaining consciousness this time, he was smiling and said, "Everything has gone. It seems different. I feel more open, doctor. I feel better than I did when I came here." When he was asked whether he still remembered his friend's face being blown off, he laughed and said, "I seem to have forgotten all about it. France is not worrying me now." When again asked whether he remembered, he said, "Yes, and the fellow with the hole in his head, but it has lifted from my mind." When asked why this was so, he replied, "I can't explain." He then started to discuss all these incidents freely, without the usual display of emotion. Later in the day he said, "I feel a lot better. It has gone out of my system. I know all about it, but it does not stick in me. It does not affect me in the same way." From this time his symptoms improved greatly.

CASE 3.—Private N. W., aged 24, had been admitted to the Thirty-Second Psychiatric Hospital in Normandy in a stuporous state with aphonia. There, abreaction was carried out under hypnosis, but this led to the development of a pronounced stammer, tics and grimacing. His history showed a fair previous personality, and he had served for three years in the army before the Normandy invasion. He was in action for several weeks, until a shell hit a tree beside which he was lying. Then he lost his voice and his symptoms developed. When first seen by us, he had a coarse, jerking, rhythmic movement of the trunk and upper limbs, and there was a severe stammer. He complained of bad dreams about an incident of mortar fire and an episode in which he had killed a German. All his life he had had an instinctual horror of killing and felt guilty in this act. He was given combined narcosis and insulin treatment for a week, with little improvement. Ether abreaction was then carried out. The patient described how he was out on patrol one night and met a patrol of Germans. He shot one of them. As he described this incident, he got more and more excited, burst out crying and went into a state of total inhibition. When he got up from the couch, his face was relaxed, he had no trace of stammer, and all jerkings had stopped. He continued to improve after this.

Cases 4 and 5 demonstrate the relief of focal cortical inhibition, such as loss of voice or stammer, early in ether excitation. The stereotypy is broken up later by carrying on the excitement to a stage of ultraboundary inhibition.

CASE 4.—Sapper P. B. K., aged 21, had received no specialized psychiatric treatment in Normandy because of the temporary pressure on beds. His history suggested a good army record, but his mother was in a hospital with a nervous breakdown, and his personality showed some anxious and hysterical trends. When we saw him first, he was unable to speak at all and pointed to his lips. He had a gross tremor of the head and upper limbs, the head jerking rhythmically from one side to the other. The shoulders were hunched up, so that the back was kyphotic. On admission he was treated with sedation for his symptoms, but this had little effect. Ether abreaction was then used. Early in the abreaction he started to talk, at first hesitantly. Then his face became red, and gradually he became more emotional. He started to shout loudly and struggle violently as he went over scenes in a mine field in which some friends had been killed. His excitement was stimulated by the therapeutist. Finally he passed into an inhibitory phase. When he regained consciousness and got off the couch, he burst into a broad smile and continued talking freely. His jerkings were less and disappeared entirely in an hour.

CASE 5.—Private C. R. R., aged 22, had been admitted to a field dressing station with difficulty in speaking, mental confusion and complaints of feeling dizzy. His history showed some neurotic traits but no actual breakdown. In the previous year his wife and baby had been

burned to death in an accidental fire, and before that he had lost a younger brother. He had carried on successfully for some weeks under shell fire in Normandy and had broken down when a shell fell near him and killed friends. He had some sedation in Normandy, but when we saw him he had gross jerkings of the limbs and head and a severe stammer. He crouched on the floor at the sound of planes. Continuous sleep for a week improved the general condition, but at the end the stammer and jerking movements continued. Ether abreaction was now used. He described how the dead brought in after his first bombing experience reminded him of his own dead wife and child. He also described being shelled in a chateau. He finally became intensely excited while relating the final incident before his breakdown, when his friends had been killed and wounded. "I ran and ran and lost my voice." This phase of great excitement occurred some time after his stammer had cleared, earlier in the abreaction. It was itself followed by a phase of inhibition. On recovery from this, his speech was normal, and all jerkings had stopped.

CASE 6.—This case illustrates the combined use of sodium amytal and ether to produce a more controlled and effective type of abreaction in a very excited patient and the symptomatic relief obtained when the ultra-paradoxic phase was finally brought about.

Sergeant J. H. T., aged 25, also came from the Thirty-Second Psychiatric Hospital in Normandy. The notes of his record showed that he had broken down after he learned that his mate had been killed. Both had been blown up by a mortar bomb after a week's shelling and mortar fire, and his friend had been badly mangled.

His history was that of a timid child, easily upset by accidents and the sight of blood and fainting easily. His previous army record was good. He had gained rapid promotion as a small arms instructor and had been four years in the service. Prior to his breakdown, the sight of dead bodies in Normandy had always upset him.

His illness first took the form of a depression with retardation and paranoid features. For this, he had been given sedatives in Normandy, with temporary benefit. Then he had become excited, started to stammer and had hysterical hallucinations of battle scenes and ideas of reference. He lost his voice coming over on the boat to England. When we first saw him, he was disheveled and agitated, and there were wild and incoordinated jerkings of the body and arms. He had a "to and fro" rocking movement of the trunk and repeatedly banged his chest with his fist. Sometimes he held a photograph of his fiancée in his hand and at other times he tucked it under his pillow or in his pajama jacket.

When ether abreaction was first tried, it brought back his voice, but he became more overactive and excited than ever. An ultraparadoxic phase did not occur. Some hours afterward his jerking movements were worse, and he had lost his voice again. This time therefore he was given an intravenous injection of sodium amytal to reduce the general excitement and bizarre behavior. It helped in this way but did not restore his voice. A second ether abreaction was now carried out while he was still under the effects of amytal. This brought about a release of much pent-up emotion. He burst into tears, and his voice again returned. Then he began to shout out his story, and he was stimulated to bring about the ultra-paradoxic phase. Suddenly he fell back inert and motionless. On recovery, he was able to speak fairly well and carried on his first rational conversation. Before treatment he had presented a bizarre and almost psychotic picture; now all jerking movements had stopped. Later he was able to write the first letter to his fiancée since his illness. While under observation for the next few days he maintained this improvement.

CASE 7.—This case shows that artificially induced excitation under ether will relieve symptoms of hysterical stupor. There is no need to produce in detail abreaction of a patient's previous battle experiences to achieve this. The case also shows that a detailed recital of battle experiences under hypnosis with sodium amytal may have little effect without the production of excitation.

Sapper J. H. H., aged 43, landed in Normandy on D day and carried on for several weeks under severe stress, until he collapsed. He remembered no more until he found himself in the Thirty-Seventh Psychiatric Hospital in Normandy. He complained of headaches and giddiness. He could not sleep and was tremulous. Sedation was given. He finally arrived back in England on a stretcher, in a state of stupor. He did not answer questions unless pressed to do so, when he might say, "Better," or shake his head. Except for showing fear reactions to aircraft passing overhead, he lay inert all day with his eyes closed. He had to be fed. If he was set up in bed, his head jerked rhythmically.

Soon after admission he was given an injection of sodium amytal intravenously. He gave a full account of himself under the action of the drug. He had been clearing mines at Caen under mortar and shell fire and was much upset at coming across the dead bodies of women and children killed in bombing raids. He was caught in a raid himself, and later several of his friends were blown up and killed by exploding mines. He finally collapsed when he was exposed to machine gun fire. As soon as the effects of the amytal had worn off, he was back in his old state. It was impossible to get anything out of him in the ensuing week. He could not stand and, if spoken to forcefully, might reply, "Better, better, better. . . . ." If he was given a tooth brush, he made constant repetitive movements across his lips. Everything was done in a stereotyped fashion. He was also incontinent, and the only spontaneous activity shown was crouching under the bedclothes if planes passed over the hospital. During another fortnight he failed to respond either to narcosis or to modified insulin treatment. His condition was therefore unchanged three weeks after his admission.

Ether abreaction was now used for the first time. It produced an immediate alteration in behavior. He began to struggle and shout and imagined he was back in Normandy. He went into repeated states of excitement, followed by momentary inhibition. He never went over his experiences in detail, as he had done with amytal. All that was obtained were isolated incidents, rather jumbled up, in his confusion. When the abreaction was stopped, he got up from the stretcher, and from that time he carried on a normal conversation and behaved normally in the ward. A few days later he was again placed under modified insulin treatment to improve his physique. One morning he suddenly relapsed into stupor with only a small dose of insulin while a flight of bombers was going overhead. He did not come out of the stupor on administration of dextrose, either by mouth or by vein. He was therefore given ether again, and it was suggested forcefully to him that he was back at Caen. He became excited very quickly, got up and walked back to the ward. A similar thing happened again a day or two later. This time ether alone did not succeed in bringing him out of the stupor, but stimulation under a combination of ether and amytal was successful. After this his condition became stabilized, and he had no further attacks of stupor in the following month.

SUMMARY

The clinical observations on a group of patients with acute war neuroses seen at the time of the Normandy invasion are compared with the observations of Pavlov on his experimental animals with regard to their symptoms and treatment. Special attention is also given to the mechanism of therapeutic abreaction in the light of Pavlov's work. Case records illustrate some of the points discussed. The concern of this paper is not so much with any particular terminology which has been used to describe our observations as with certain broad mechanistic principles which may underlie a variety of phenomena hitherto widely separated. Further investigations along these lines may show a rational basis for the greater coordination of various aspects of psychiatric treatment.

Dr. Eliot Slater assisted in the formulation and composition of this paper. Dr. Louis Minski, of the Sutton Emergency Hospital, Surrey, and Dr. Joshua Carse, of Summerdale Emergency Hospital, Chichester, Sussex West, made available treatment facilities, enabling the work to be carried out.

Sutton Emergency Hospital Neuropsychiatic Unit, Brighton Road, Sutton, Surrey, England.

# DISTURBANCES IN SLEEP MECHANISM: A CLINICOPATHOLOGIC STUDY

## II. LESIONS AT THE CORTICODIENCEPHALIC LEVEL

CHARLES DAVISON, M.D.
NEW YORK
AND
MAJOR EDWIN L. DEMUTH
MEDICAL CORPS, ARMY OF THE UNITED STATES

The rarity of disturbances in sleep in patients with pure cortical lesions, as previously reported by us [1] and by others, is in marked contrast to the frequency of their occurrence in patients with lesions involving both the cortex and the diencephalon.

Discrete lesions of the hypothalamus are known to cause interference with normal regulation of sleep. A brief review of the experimental and clinical evidence will be given in a later publication, concerned essentially with lesions at this level. Experimental evidence that lesions at the corticodiencephalic level may be responsible for disturbances in sleep is scanty. Clinical evidence, however, as furnished by the 25 cases in this presentation, and by the reports of other investigators, indicates that lesions at this level, involving either the centers or their pathways, are not of uncommon occurrence. In many of the cases to be discussed it was difficult to determine whether somnolence was the result of the disease of the cortex or of the diencephalon or of both.

### REPORT OF CASES

CASE 1.—*Glioblastoma multiforme of the left temporal lobe and basal ganglia; compression and invasion of the infundibular region with pathologic changes in the hypothalamus. Somnolence. Increased intracranial pressure.*

S. F., a girl aged 18 years, slept most of the day and night but could be aroused. There were two episodes of sudden loss of consciousness of twenty-four hours' duration. Craniotomy revealed a neoplasm of the left temporal lobe. The somnolence disappeared, to return later. She was operated on again, but the somnolence persisted.

*Neurologic Examination.*—There were aphasia, paralysis of the right side of the body with pyramidal tract signs, contraction of the right half of the visual fields and pronounced secondary atrophy of the optic nerves.

*Laboratory Data.*—The blood urea nitrogen level was normal. The temperature was often 97 F. The cerebrospinal fluid was under a pressure of 280 mm. of water. The spinal fluid contained 4 lymphocytes per cubic millimeter and 145 mg. of protein per hundred cubic centimeters.

*Autopsy.*—There were destruction and invasion of the left third frontal and temporal convolutions, the basal ganglia and external capsule and part of the hypothalamus, especially the region of the tuber cinereum (fig. 1). All of the diencephalic structures on the left side were compressed. The entire ventricular system and the aqueduct of Sylvius were greatly dilated. The various nerve cells of the left hypothalamus were diminished in number. These cells showed chromatolysis, severe cell changes of Nissl and loss of iron pigment. The nerve cells of the right hypothalamus disclosed slight chromatolytic changes.

*Comment.*—The lethargy in this case was undoubtedly caused by the compression and invasion of the hypothalamus. It cannot be stated with certainty that involvement of the cortex and the basal ganglia was not a contributory factor.

CASE 2.—*Glioblastoma multiforme of the frontal motor and temporal convolutions, corpus callosum and basal ganglia on the left side, with compression of the hypothalamus and pathologic changes. Drowsiness. Increased intracranial pressure.*

K. N., a man aged 45, gave a history of convulsions, headaches, drowsiness, apathy and projectile vomiting.

*Neurologic Examination.*—Examination disclosed amaurosis bilaterally, papilledema, diplopia, right flaccid hemiplegia with pathologic reflexes, poor memory, anomia and drowsiness, from which he could be aroused. His vocabulary consisted of "yes" and "no." He could follow simple commands.

*Laboratory Data.*—The cerebrospinal fluid pressure was 240 mm. of water. The spinal fluid was clear, contained 9 cells per cubic millimeter and had a total protein content of 38 mg. per hundred cubic centimeters. The temperature was occasionally 97 F.

From the Neuropsychiatric Service and the Neuropathological Laboratory of the Montefiore Hospital, and the Neurological Department of Columbia University College of Physicians and Surgeons.

A report on this study, of which the present paper is the second section, was made before the Chicago Neurological Society on May 20, 1943, and before the New York Academy of Medicine, Section of Neurology and Psychiatry, on Feb. 8, 1944. An abstract of the paper, with discussion, was published in the January 1944 issue of the ARCHIVES, page 79.

1. Davison, C., and Demuth, E. L.: Disturbances in Sleep Mechanism: I. Lesions at the Cortical Level, Arch. Neurol. & Psychiat. **53**:399 (June) 1945.

*Course of Illness.*—After craniotomy and removal of part of the cerebral neoplasm, the patient was in a state of torpor for four days, from which he could be awakened. Then he began to speak spontaneously but perseverated. Later he became somnolent again.

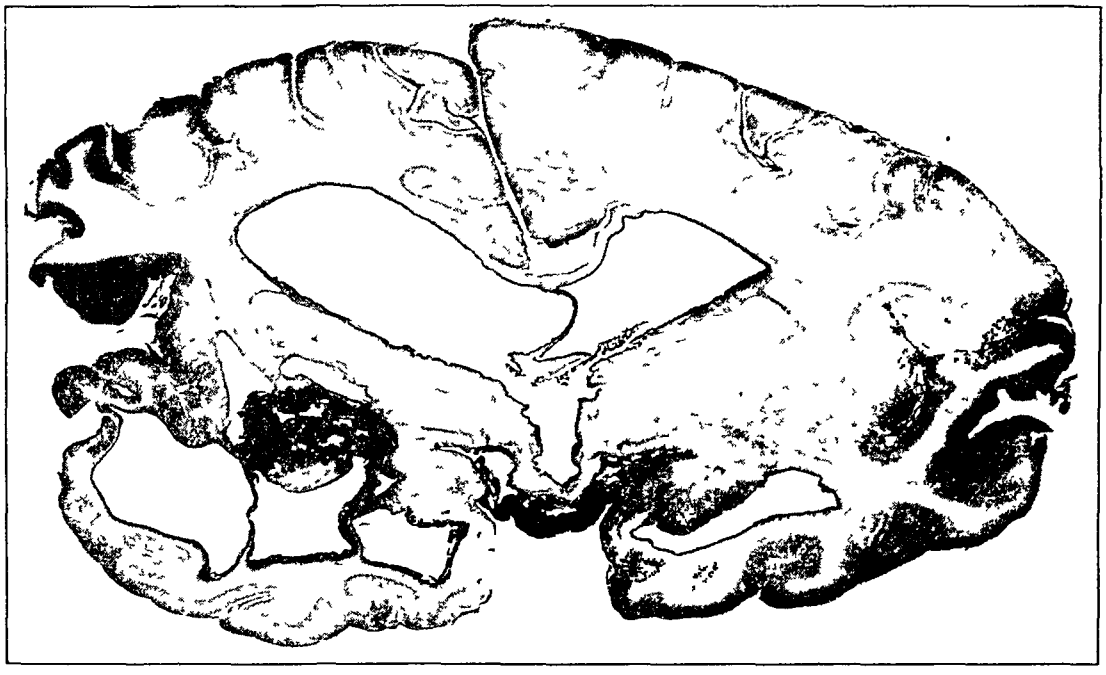


Fig. 1 (case 1).—Glioblastoma multiforme of the left temporal lobe and basal ganglia. Notice invasion of the infundibular region and compression of the hypothalamus.

Fig. 2 (case 2).—Glioblastoma multiforme of the left frontal, motor, parietal and temporal convolutions, the corpus callosum and the basal ganglia, with compression of the hypothalamus.

*Autopsy.*—The left third frontal, motor, temporal and part of the inferior parietal convolution and the left portion of the corpus callosum were replaced with tumor tissue, which was necrotic in places. The left lateral ventricle was constricted and distorted; the third ventricle was dilated. The thalamic nuclei, the striatum and the pallidum on the left side were partly destroyed, and the hypothalamus was compressed (fig. 2). The various hypothalamic nerve cells, especially in the left posterior half, were diminished in number and showed chromatolysis, vacuolation and severe cell changes of Nissl.

*Comment.*—In this instance the drowsiness was probably caused by the changes in the hypo-

thalamus and by involvement of the cortico-hypothalamic and striohypothalamic pathways.

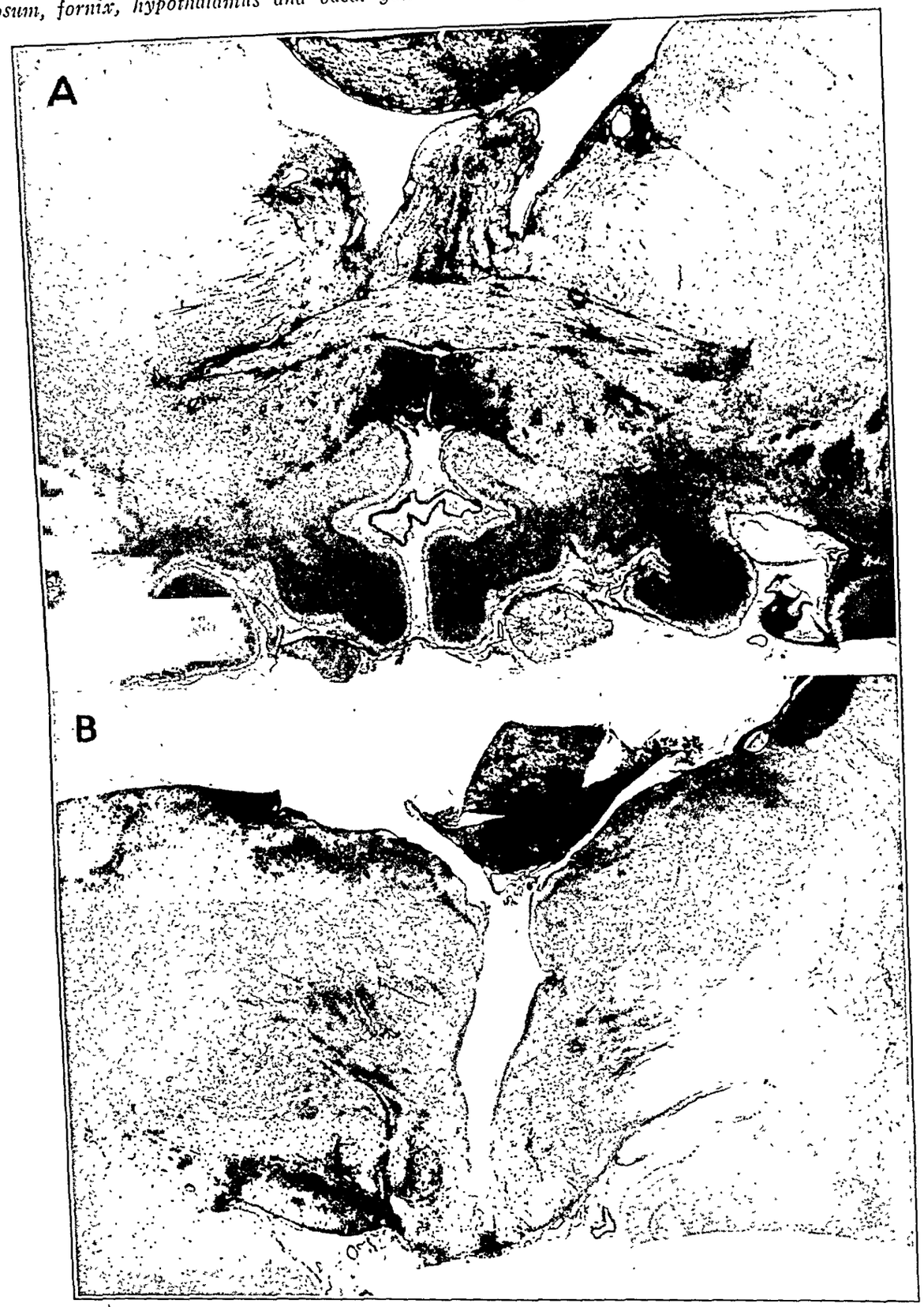
CASE 3.—*Lymphosarcoma with metastases to the corpus callosum, fornix, hypothalamus and basal ganglia. Korsakoff's syndrome with lethargy. No clinical evidence of increased intracranial pressure.*

C. L., a woman aged 40, had lymphosarcoma, and mental symptoms and lethargy developed.

*Neurologic Examination.*—There were a typical Korsakoff syndrome, bilateral intention tremor of the extremities and adiadokokinesis of the right upper extremity. The patient was first lethargic and later became stuporous but could always be aroused.

*Laboratory Data.*—The blood sugar measured 107 mg. and the urea nitrogen 13 mg. per hundred cubic centimeters. The cerebrospinal fluid was not examined.

*Autopsy.*—There were lymphosarcomatous perivascular infiltrations in the corpus callosum, the fornix, the anterior commissures, all of the hypothalamic nuclei and the pallidal segments (fig. 3 *A* and *B*.)




g. 3 (case 3).—Lymphosarcomatous invasion of the corpus callosum, the fornix, the preoptic region and the anterior commissura (*A*) and invasion of the pallidum and the hypothalamic region (*B*).

*Comment.*—This case is placed in the corticodiencephalic group because of the lesions in the corpus callosum and the fornix. The latter is considered a direct corticohypothalamic tract. Were it not for this, the case could be regarded as an example of a pure hypothalamic lesion. There was also striohypothalamic involvement, as a result of invasion of the pallidum.

CASE 4.—*Glioblastoma multiforme of the left frontal and parietomotor convolutions without compression of or pathologic changes in the hypothalamus but with involvement of the basal ganglia. Periods of somnolence. Increased intracranial pressure.*

L. J., a man aged 30, in driving his car, had to stop frequently because of an overwhelming urge to sleep. This somnolence would persist for a few seconds. The attacks continued for five months, with increasing drowsiness, until vision was diminished and headache and vomiting developed. He had to sleep at frequent intervals during the day but could be easily aroused.

*Neurologic Examination.*—There were bilateral papilledema, generalized hyporeflexia and inability to concentrate.

*Laboratory Data.*—The urea nitrogen level was normal. Manometric studies revealed an initial pressure of 220 mm. The spinal fluid was xanthochromic, with numerous red blood cells and a 4 plus Pandy reaction.

*Course.*—An infiltrating glioblastoma multiforme in the left prerolandic area was partially removed, with disappearance of the somnolence. Within six months the somnolence recurred.

*Autopsy.*—There was a glioblastoma multiforme of the left frontal, motor and orbital convolutions and the corpus callosum (fig. 4). The basal ganglia on the left side were compressed, and the internal capsule, putamen, claustrum, external capsule and entire island of Reil on that side were destroyed. The various hypothalamic nerve cells were normal except for some diminution in heavy iron pigment.

*Comment.*—Although the hypothalamus was not affected, the involvement of the cortex and the basal ganglia places the case in the corticodiencephalic group.

CASE 5.—*Glioblastoma multiforme of the right frontal and motor regions, extending into the basal ganglia; compression of but no pathologic changes noted in the hypothalamus. Somnolence. Increased intracranial pressure.*

S. L., a man aged 47, had jacksonian seizures and paralysis of the left upper extremity, progressive diminution in vision, headaches and somnolence.

Fig. 4 (case 4).—Glioblastoma multiforme of the left frontal, motor and parietal region, invading the corpus callosum and destroying and compressing part of the basal ganglia The hypothalamus was not invaded.

*Neurologic Examination.*—There were left hemiplegia with pathologic reflexes; bilateral atrophy of the optic nerve; slight irregularity of the left pupil, which was larger than the right, and somnolence, from which the patient could be aroused.

*Laboratory Data.*—Lumbar tap disclosed an initial pressure of 180 mm. of water. All other examinations gave normal results.

*Autopsy.*—A glioblastoma multiforme involved the right frontal and motor convolutions. The neoplasm extended into the island of Reil, the internal capsule, the putamen and the pallidal segments. The hypothalamus appeared normal.

*Comment.*—In this case the involved corticodiencephalic and striodiencephalic pathways were probably responsible for the somnolence.

CASE 6.—*Glioblastoma multiforme of the left premotor, motor and parietal regions, with invasion of the basal ganglia and thalamus on the left side; compression of and pathologic changes in the hypothalamus. Attacks of unconsciousness. Increased intracranial pressure.*

S. G., a man aged 34, first experienced jacksonian seizures of the right upper extremity, followed later by attacks of unconsciousness, from which he could be partially aroused. There was bilateral papilledema. After operation and radiation therapy, the disease progressed, with frequent generalized convulsions and loss of consciousness.

*Laboratory Data.*—Urinalysis revealed a 4 plus reaction for albumin. The blood urea nitrogen measured 13 mg. and the sugar 96 mg., per hundred cubic centimeters. The spinal fluid was xanthochromic; there was a positive Pandy reaction; the total protein content was 257 mg. per hundred cubic centimeters, and the cell count was 35 per cubic millimeter. The pressure was not recorded.

*Autopsy.*—A tumor in the left premotor, motor and parietal regions involved the corpus callosum, the basal ganglia and the thalamus and compressed the hypothalamic nuclei. The nerve cells of the hypothalamus, especially on the left, showed various pathologic changes.

CASE 7.—*Spongioblastoma polare of the right frontal and motor regions; compression of the striatum but not of the hypothalamus. Attacks of unconsciousness and somnolence. Increased intracranial pressure.*

R. M., a man aged 74, suffered from impaired vision, headaches and attacks of unconsciousness and somnolence. He would lose consciousness and fall to the ground without warning. He could be awakened from some of these attacks but not from others. There were bilateral papilledema and rigidity.

*Laboratory Data.*—The urine and blood chemistry were normal. Examination of the spinal fluid revealed no cells, 88 mg. of protein per hundred cubic centimeters and an initial pressure of 220 mm. of water.

*Autopsy.*—A large spongioblastoma was situated in the right third frontal and motor convolutions and extended as far as the external capsule, impinging on the right putamen. The hypothalamus did not appear compressed, and its nerve cells showed no pathologic changes.

*Comment.*—The hypothalamus in this case did not show pathologic changes. The disturbance of sleep was the result of involvement of the corticodiencephalic or of the striohypothalamic pathways.

CASE 8.—*Abscess of the right frontal, orbital, motor and temporal convolutions, invading the internal capsule, the putamen and part of the pallidum; slight compression of the hypothalamus, with minor changes limited to the preoptic region. Lethargy. Increased intracranial tension.*

C. S., a man aged 23, complained of persistent pain over the right eye and nose following an infection of the upper respiratory tract. He became drowsy but could be aroused.

*Neurologic Examination.*—There were nuchal rigidity, a bilateral Babinski sign, mimetic movements of the left side of the face and blurring of the left disk margin.

*Course.*—Spinal tap disclosed 7 cells per cubic millimeter, a total protein content of 41 mg. per hundred cubic centimeters and an initial pressure of 340 mm. of water. The patient was facetious, very talkative and hypomanic. Aspiration of the contents of an abscess from the right frontal lobe was performed, but the lethargy persisted.

*Autopsy.*—There was an abscess in the region of the frontal, motor and temporal convolutions, the internal capsule, the putamen and part of the pallidum (fig. 5). The hypothalamus was slightly compressed, but the various nerve cells of the hypothalamic nuclei appeared normal, except for a few in the preoptic region.

*Comment.*—Although the hypothalamus did not show any pathologic changes, because of its slight compression and the involvement of the basal ganglia, there is justification for including this case in the corticodiencephalic group. The role played by the striohypothalamic fibers, as in a few of the other cases in this group, cannot be entirely excluded.

CASE 9.—*Encephalitis lethargica. Diffuse involvement of the cortex, basal ganglia and diencephalon. Periods of somnolence. No evidence of increased intracranial pressure.*

P. H., a boy aged 7 years, had fever and periods of drowsiness. Later there appeared generalized myoclonic movements and difficulty in speech.

*Neurologic Examination.*—There were choreiform and myoclonic movements of the whole body, especially the face and the upper extremities. The patient was drowsy but could be aroused. The pupils reacted to light and in accommodation.

*Laboratory Data.*—Spinal tap disclosed an initial pressure of 150 mm. There were no cells, and the total protein measured 41 mg. per hundred cubic centimeters. The blood chemistry was normal. The temperature varied between 97 and 101 F.

*Autopsy.*—A widespread encephalitic process extended throughout the central nervous system, including the cortex, the basal ganglia, the thalamic and hypothalamic nuclei (fig. 6), the mesencephalon and the metencephalon.

*Comment.*—Although the lesions were diffuse, those in the hypothalamus undoubtedly played the most important role in the causation of somnolence.

CASE 10.—*Multiple cerebrovascular lesions involving branches of the middle cerebral arteries; lesions in the hypothalamus and basal ganglia. Somnolence. No evidence of increased intracranial pressure.*

S. Z., a man aged 69, suffered for four years from left hemiplegia and spontaneous laughing and crying. Toward the end of the fourth year, extreme lethargy appeared, from which he could be aroused. He lost interest in everything and wished only to sleep. When aroused, he would respond to questioning with outbursts of crying. Later, somnolence became more prolonged and profound.

*Neurologic Examination.*—There was left hemiparesis with bilateral pyramidal tract signs, palsy of the right side of the face of central type and impairment of mental functioning.

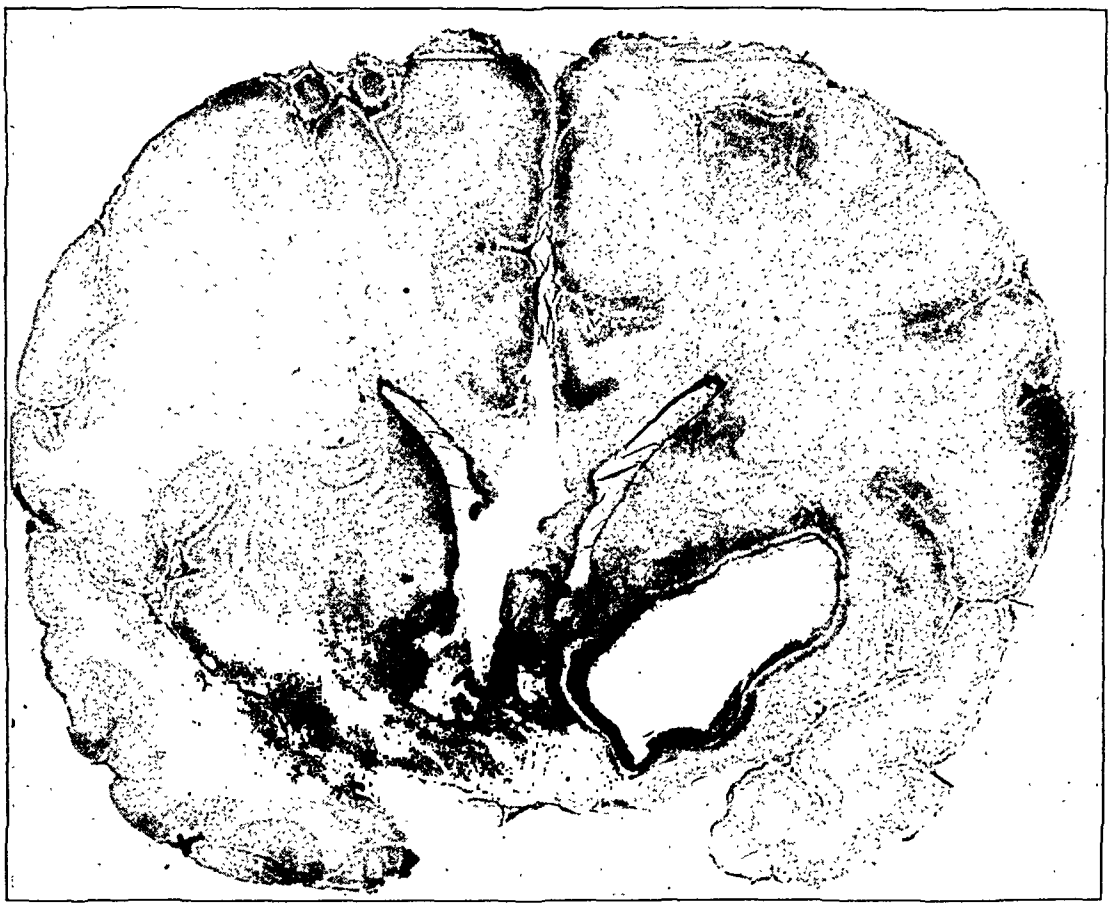


Fig. 5 (case 8).—Abscess of the right frontal and orbital convolutions, compressing and slightly invading the putamen and part of the pallidum, with compression of the preoptic region.

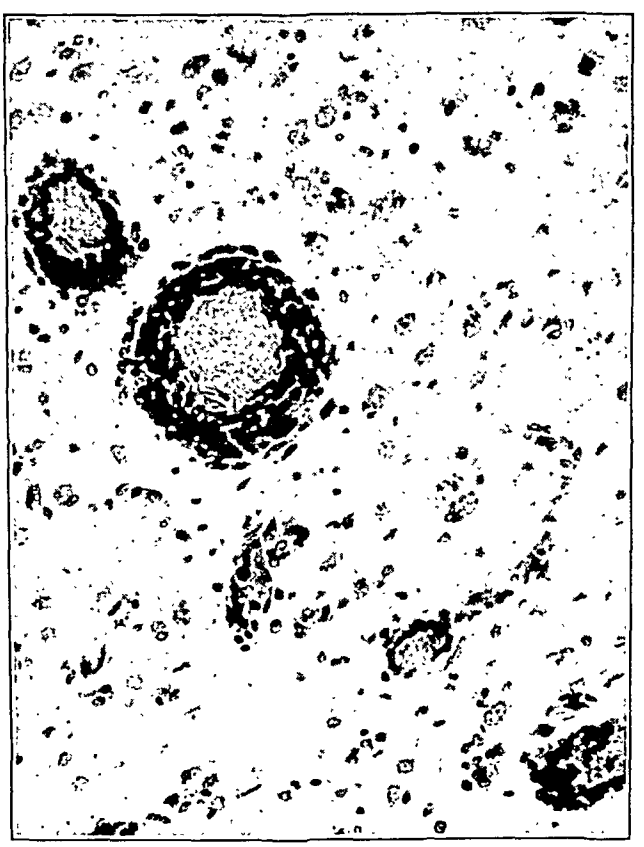


Fig. 6 (case 9).—Perivascular infiltration in the diencephalon in a case of encephalitis lethargica.

*Laboratory Data.*—The blood chemistry was normal. The spinal fluid contained 13 cells, all lymphocytes, per cubic millimeter; the Pandy reaction was negative, and the initial pressure was 120 mm. The temperature ranged from 97 to 98 F., occasionally falling to 96 and once to 95 F.

*Course.*—The patient had episodes of explosive weeping, although generally he appeared cheerful and happy. His lethargy deepened, and he lost interest in his surroundings. He finally became cataleptic.


Fig. 7 (case 10).—Multiple cerebrovascular lesions involving branches of the middle cerebral arteries, with lesions of various convolutions, the internal capsule, the basal ganglia and the hypothalamus.

*Autopsy.*—There were several areas of softening along the distribution of both middle cerebral arteries with involvement of various convolutions, the internal capsule and the striatum (fig. 7). Throughout the basal ganglia and the hypothalamus, there was calcification of the vessels with areas of devastation. In the hypothalamus, some of the nerve cells of the nucleus paraventricularis, the nucleus supraopticus, the nucleus reuniens and the tuber cinereum were destroyed by this process.

*Comment.*—The somnolence was probably the result of hypothalamic lesions. Corticohypothalamic or striohypothalamic involvement, however, cannot be ruled out.

CASE 11.—*Diffuse syphilitic encephalitis involving the cortex and the diencephalic nuclei. Somnolence. No evidence of increased intracranial pressure.*

S. A., a man aged 72, presented impairment in memory for past and recent events, disorientation and somnolence.

*Neurologic Examination.*—The patient was semistuporous but responded to noxious stimuli. The pupils reacted to light and in accommodation.

*Laboratory Data*—The blood urea nitrogen measured 30 mg. per hundred cubic centimeters; the Wassermann reaction of the blood was 4 plus and the Kahn reaction 2 plus. The Wassermann reaction of the spinal fluid was 4 plus; the gum mastic curve was 555442100. The recordings of the spinal fluid pressure were not given, but it was stated that they were normal.

*Autopsy.*—There was generalized atrophy of the convolutions, particularly the frontal. A diffuse inflammatory process was present in the cortex and the diencephalic nuclei. Some of the nerve cells of the hypothalamic nuclei showed pathologic changes, such as shrinkage, chromatolysis, loss of iron pigment and complete destruction.

CASE 12.—*Glioblastoma multiforme, extending from the right frontal to the occipital convolutions; compression of the basal ganglia and hypothalamus, with pathologic changes in the nerve cells. Episodes of drowsiness. Increased intracranial pressure.*

C. C., a man aged 37, had convulsive seizures with loss of consciousness. Later developments included personality changes, loss of libido and drowsiness. He would continually fall asleep at any time during the day, sleeping for irregular periods, but he could be aroused on questioning. There then developed failing vision, with bilateral choked disk, projectile vomiting, bilateral pyramidal tract signs and sensory disturbances on the left side. Craniotomy revealed a glioblastoma multiforme in the right frontoparietal area. The drowsiness increased after the operation. The temperature was often 97 F. and once 96.6 F.

*Laboratory Data.*—The cerebrospinal fluid was under a pressure of 240 mm.; it contained 15 cells per cubic millimeter and 80 mg. of protein per hundred cubic centimeters.

*Autopsy.*—The gray and white matter on the right side, from the frontal to the occipital convolutions, were infiltrated with a glioblastoma multiforme. In sections through the diencephalic nuclei, in addition to destruction of the respective convolutions, there was involvement of the putamen, the pallidum, the internal and external capsules, the insula and part of the thalamic nuclei on the right side. The hypothalamic nerve cells on this side showed shrinkage, disintegration of Nissl substance and pronounced loss of iron pigment.

*Comment.*—The sleepy state in this instance was probably caused either by involvement of the corticodiencephalic and striohypothalamic pathways or by the compression of the hypothalamus.

CASE 13.—*Glioblastoma multiforme of the left frontal, temporal and parietal convolutions and basal ganglia;*

*compression of the posterior hypothalamus. Recurring lethargy. Increased intracranial pressure.*

L. S., a man aged 54, in addition to many neurologic symptoms, had sudden episodes of lethargy, from which he could be aroused. These attacks were associated with a slow pulse of 60 per minute. The patient's condition improved, and his lethargy disappeared. He was then considered to have chronic encephalitis. Six weeks later, however, there was a return of the lethargy, followed by semistupor. There was bilateral papilledema. Spinal tap disclosed an initial pressure of 150 mm., and there was an increase in globulin.

*Autopsy.*—A tumor was found in the left second and third frontal convolutions. Sections through the insula and basal ganglia revealed two tumors—one situated in the left temporal and parietal lobes and the other in the white mater directly above it, involving the putamen, the globus pallidus and the island of Reil. The various hypothalamic nuclei on the left were compressed and distorted, and their nerve cells, especially in the posterior half, showed all types of pathologic changes, such as complete destruction, shrinkage and loss of chromatin and of heavy iron pigment.

*Comment.*—In this instance, the somnolence and other symptoms could easily be accounted for by the frontal and temporal neoplasm, which extended into the basal ganglia and partially compressed the various hypothalamic nuclei, especially those of the posterior half.

CASE 14.—*Glioblastoma multiforme of the right temporal lobe; compression of the basal ganglia and hypothalamus with pathologic changes in its nerve cells, especially in the posterior half. Somnolence. No evidence of increased intracranial pressure.*

K. D., a man aged 52, frequently fell asleep after supper, a most unusual procedure for him. Later, marked changes in behavior, confusion, deliriousness and drowsiness were noted.

*Neurologic Examination.*—The patient was in stupor, from which he could be aroused with difficulty. There were hyperactive reflexes, normal fundi and slightly irregular pupils, which reacted sluggishly to light.

*Laboratory Data.*—The blood urea nitrogen measured 19 mg. per hundred cubic centimeters. The spinal fluid was clear and contained no cells; the total protein content was 39 mg. per hundred cubic centimeters, and the initial pressure was 120 mm. of water.

*Autopsy.*—A glioblastoma multiforme had destroyed practically all of the right temporal convolutions and part of the insula. There was slight compression of the diencephalon and the basal ganglia on the right side (fig. 8). The hypothalamic nerve cells, especially of the right posterior half, were diminished in number and showed chromatolysis, loss of pigment granules and severe cell changes of Nissl. The nerve cells on the left side were better preserved.

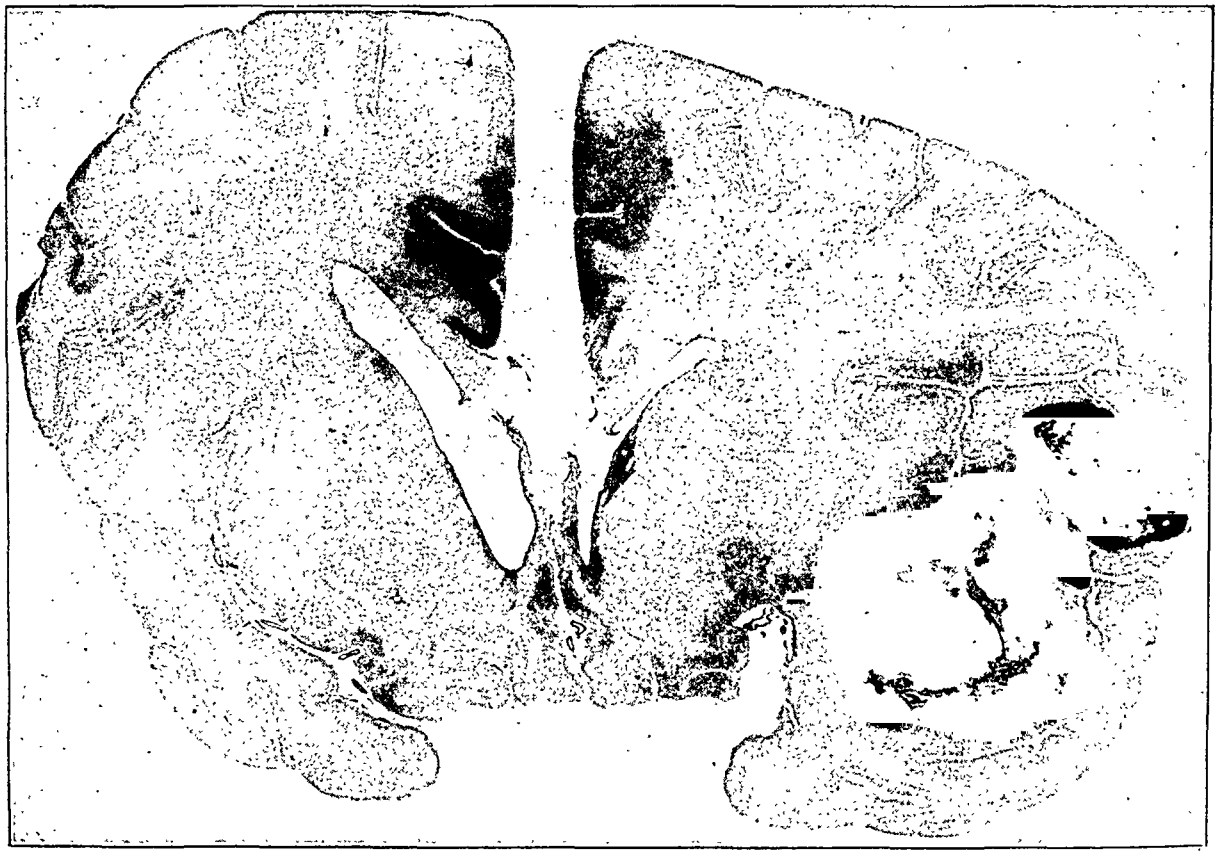


Fig. 8 (case 14).—Glioblastoma multiforme of the right temporal lobe, with compression of the basal ganglia and the hypothalamus.

*Comment.*—Although the tumor was limited mainly to the cortex, there was also compression of the diencephalon and the basal ganglia, with pathologic changes in the posterior half of the hypothalamus to account for the drowsiness. This patient was one of the few whom it was difficult to arouse.

CASE 15.—*Astroblastoma of the left motor and parietal regions; compression of the basal ganglia and hypothalamus, without changes in the nerve cells of the hypothalamus. Lethargy, which cleared up after removal of the tumor; recurrence later. Increased intracranial pressure.*

K. I., a man aged 50, gave a history of headaches and spells of confusion and drowsiness, from which he could be aroused.

*Neurologic Examination.*—Papilledema was present bilaterally; the left pupil was smaller than the right, and there was right homonymous hemianopsia, with sparing of the macula.

*Course.*—A craniotomy was performed, and an astroblastoma was removed from the left temporoparietal region, after which the lethargy cleared up for a few weeks but recurred later.

*Laboratory Data.*—Examination of the spinal fluid disclosed 2 cells per cubic millimeter, a positive Pandy reaction, a total protein content of 58 mg. per hundred cubic centimeters and an initial pressure of 360 mm. The blood chemistry was normal, and the other data were not remarkable.

*Autopsy.*—An extensive neoplasm destroyed part of the white matter from the motor to the end of the parietal region on the left side. The basal ganglia and the hypothalamic structures on the left were slightly compressed. There was, however, no evidence of any pathologic changes in the nerve cells of the hypothalamus, except for some loss in iron pigment granules.

*Comment.*—Although the tumor was limited to the motor and parietal regions, there was some compression of the basal ganglia and the hypothalamic nuclei on the left side, without any evidence of changes in the nerve cells. It is possible that pressure on the striohypothalamic pathways might have led to the state of lethargy.

CASE 16.—*Carcinoma of the lung with metastases to the right parieto-occipital region; compression of the basal ganglia and the posterior half of the hypothalamus with changes in its nerve cells. Lethargy. No evidence of increased intracranial pressure.*

A. A., a woman aged 37, gave a history of diplopia, frontal headaches, nonprojectile vomiting, myoclonic twitching on the left side of the body, numbness of the left hand and lethargy, from which she could be aroused. At this time, a diagnosis of lethargic encephalitis, was considered.

*Neurologic Examination.*—Examination disclosed left hemiparesis with pathologic reflexes, left hemihypalgesia, bilateral ptosis, convergent squint, total external ophthalmoplegia, irregular pupils, which did not react to light and in accommodation, anesthesia of the left cornea, masked facies and difficulty in opening the jaw.

*Laboratory Data.*—A spinal tap showed clear fluid under normal pressure. The blood chemistry was normal.

*Autopsy.*—The right parietal and occipital lobes were replaced by a large cystic tumor, which compressed and destroyed part of the putamen and the globus pallidus. The hypothalamus on the same side was compressed. The various hypothalamic nerve cells, especially in the posterior half, were diminished in number and showed loss in chromatin and absence of iron pigment.

*Comment.*—The lethargy in this case was at first considered to be the result of lethargic encephalitis, but at necropsy it was demonstrated to have been caused by a neoplasm involving the cortex and the basal ganglia and compressing the hypothalamus. As in some other cases, the nuclei of the ocular nerves were involved.

CASE 17.—*Carcinoma of the breast with diffuse metastases in the central nervous system, including the basal ganglia and the hypothalamus. Lethargy. Increased intracranial pressure.*

G. E., a woman aged 36, had a neoplasm of the breast, which was removed. Three years later she complained of dizziness, vomiting and a desire to sleep all the time.

*Neurologic Examination.*—The patient was somnolent, from which state she could be aroused with difficulty, but she responded readily to questioning. The optic disks were blurred.

*Laboratory Data.*—The cerebrospinal fluid was not examined. The blood chemistry was normal.

*Autopsy.*—The diencephalon, basal ganglia, mesencephalon, cerebellum and occipital convolutions were infiltrated with metastases. The various hypothalamic nuclei were also invaded by the neoplasm, and their nerve cells showed all types of pathologic changes.

CASE 18.—*Astrocytoma of the right frontal, motor, parietal, temporal, hippocampal and occipital convolutions, with compression of the hypothalamus. Somnolence. Increased intracranial pressure.*

M. P., a woman aged 54, experienced headache, blurred vision, vomiting and vertigo, followed later by loss of consciousness, from which she could be aroused. There were papilledema, ptosis of the left eyelid, left hemianopsia and other neurologic signs irrelevant to the somnolence. After a craniotomy in the right parietotemporal region, there was an increased tendency to somnolence.

*Laboratory Data.*—The urine and the blood chemistry were normal. The spinal fluid showed an initial pressure of 300 mm.

*Autopsy.*—An astrocytoma involved the right frontal, motor, parietal, temporal, hippocampal and occipital convolutions. The tumor extended through the region of the splenium of the corpus callosum into the hippocampus, the fusiform gyrus and the occipital convolutions (fig. 9). Part of the lateral and inferior hypothalamic nuclei on the right side were compressed by the neoplasm (fig. 9). Some of their nerve cells showed pallor and chromatolysis.

CASE 19.—*Glioblastoma multiforme of the left temporal lobe, compressing the caudal and lateral parts of the hypothalamus. Recurring lethargy. Increased intracranial pressure.*

J. A., a man aged 38, suffered from severe frontal headache and sleepiness, from which he could be aroused. There was bilateral papilledema. His temperature was normal, and his pulse 60 per minute. A history of head trauma five months previously was elicited. Exploration for a subdural hematoma revealed a neoplasm.

*Laboratory Data.*—The spinal fluid was under an initial pressure of 360 mm. of water and contained 3 cells per cubic millimeter. The serologic reactions were positive, and the colloidal gold curve was of first zone, dementia paralytica, type.

*Autopsy.*—There was a tumor extending from the left temporal to the occipital convolutions. Part of the left caudal and lateral portions of the hypothalamus were compressed. The hypothalamic nerve cells were diminished in number and appeared "washed out." Occasional destruction of nerve cells was also noted.

CASE 20.—*Glioblastoma multiforme of the right frontal, motor and parietal convolutions; slight compression of and pathologic changes in the hypothalamus. Somnolence. Increased intracranial pressure.*

tion of 2 plus. The results of all other laboratory studies were noncontributory.

*Autopsy.*—A glioblastoma multiforme involved the right frontal, motor and part of the parietal convolutions. The hypothalamus was compressed, and the various hypothalamic nerve cells, especially on the right, showed ischemia, chromatolysis or severe cell changes of Nissl.

CASE 21.—*Glioblastoma multiforme of the left parieto-occipital region, compressing the posterior part of the*

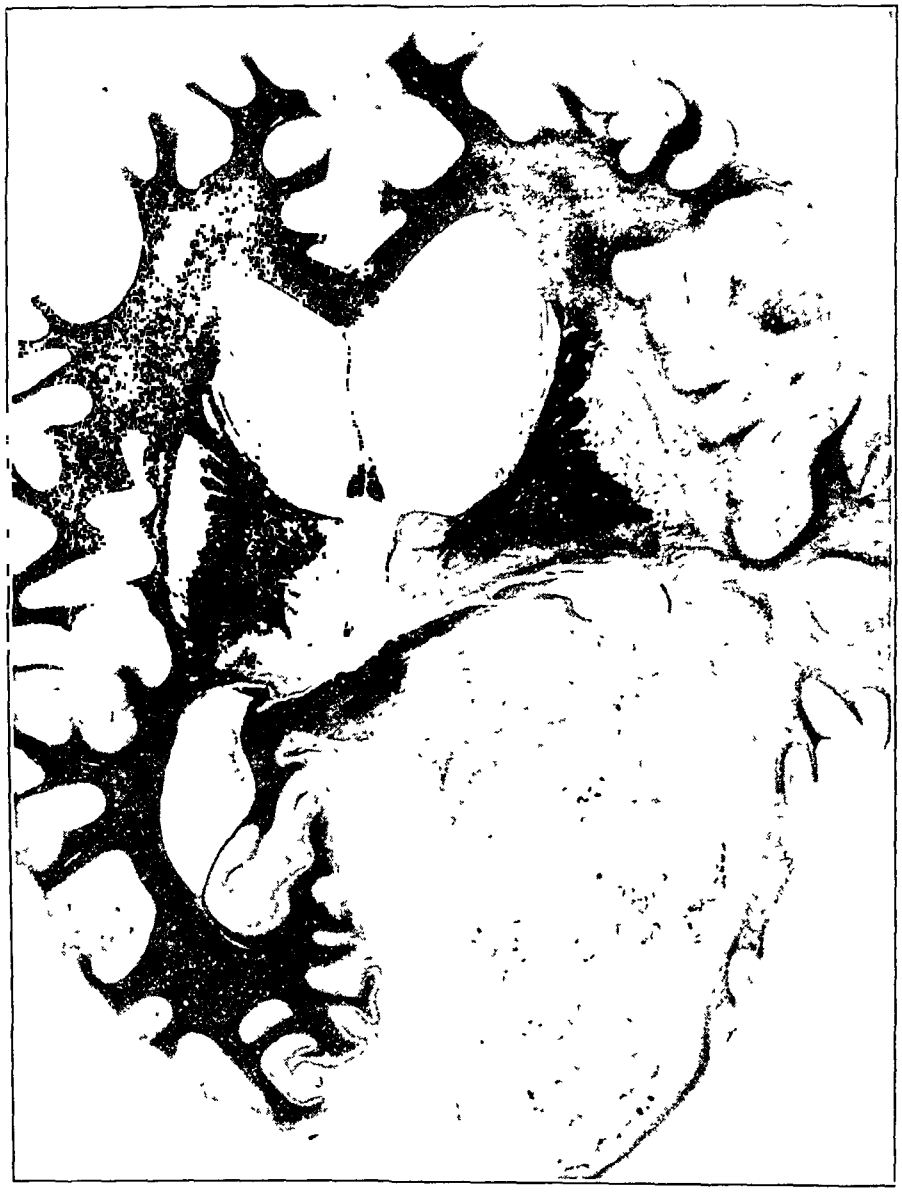


Fig. 9 (case 18).—Astrocytoma of the right occipital, hippocampal and temporal convolutions with compression, especially of the right hypothalamus.

S. L., a man aged 48, had progressive paralysis of the left arm, associated with jacksonian motor and sensory seizures. There were also headaches, twitching of the eyelids and dimness of vision. After a craniotomy, the patient became somnolent but could be aroused. In addition to other neurologic findings, there were bilateral atrophy of the optic nerve and slight irregularity of the left pupil, which was larger than the right.

*Laboratory Data.*—Spinal puncture showed an initial pressure of 450 mm. of water, a protein level of 78 mg. per hundred cubic centimeters and a Pandy reac-

*hypothalamus. Insomnia, later followed by somnolence. Increased intracranial pressure.*

V. M., a woman aged 39, complained of headaches, dimness of vision, memory defects, insomnia, vomiting, apathy and drowsiness. There was bilateral papilledema. The right pupil was larger than the left and reacted slightly less to light. Impairment of right conjugate deviation was evident. A cystic tumor was removed from the left occipital lobe at operation. The patient became progressively more drowsy and apathetic but could be aroused.

*Laboratory Data.*—The spinal fluid was under an initial pressure of 320 mm. of water.

*Autopsy.*—There was a hemorrhagic tumor in the region of the left parieto-occipital area, destroying part of the pulvinar, the entire centrum ovale and part of the white and gray matter of the fusiform gyrus and hippocampus. The hypothalamus was compressed, and the hypothalamic nerve cells, especially on the left and posteriorly, showed pathologic changes.

CASE 22.—*Suprasellar meningioma, without invasion of the sella turcica but compressing the frontal, orbital and cingular gyri and the hypothalamus. Lethargy. No evidence of increased intracranial pressure.*

K. E., a woman aged 50, suffered from sleepiness and drowsiness. She would sleep for three days continuously unless awakened. Later, there developed visual impairment, which progressed to complete blindness.

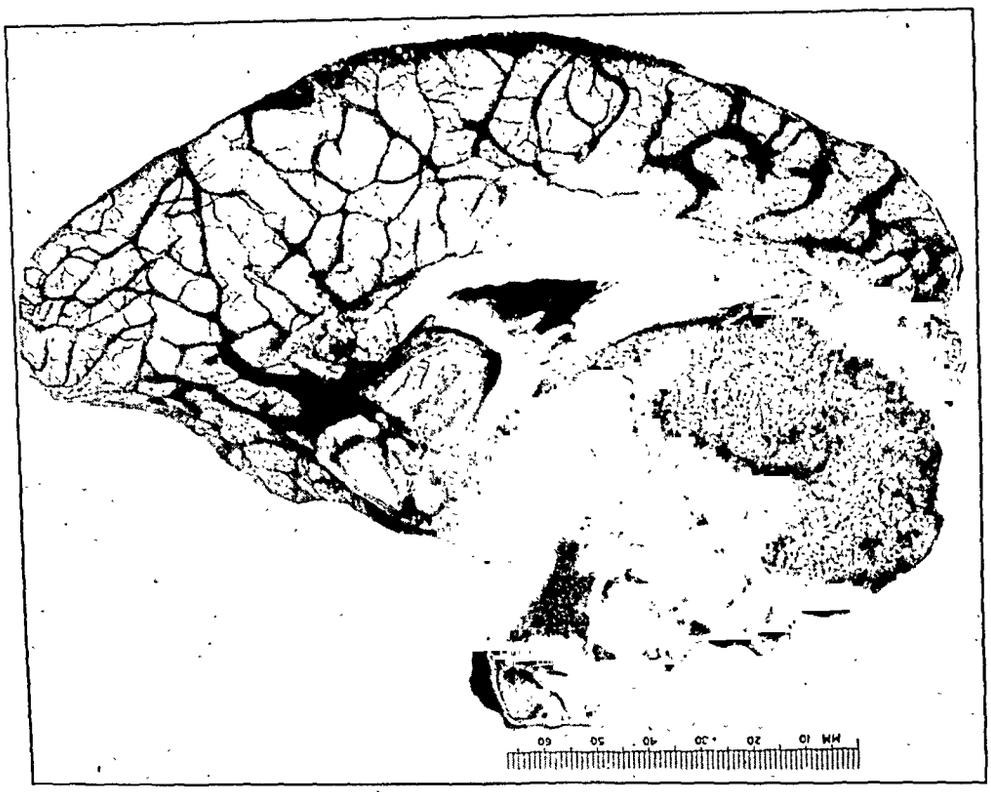


Fig. 10 (case 22).—Suprasellar meningioma compressing the frontal, orbital and cingular gyri and the hypothalamus.

*Neurologic Examination.*—The patient was completely disoriented, and her mood varied between joviality and violence. She slept and yawned most of the time but could be aroused. There were jargon aphasia, bilateral atrophy of the optic nerve, with complete amaurosis, and generalized hyperreflexia. The temperature ranged from 97 to 98 F.; once it was 96.6 F. There were no endocrine disturbances.

*Laboratory Data.*—The serologic reactions of the blood and spinal fluid were negative. The spinal fluid was clear, contained 3 cells per cubic millimeter and showed an initial pressure of 80 mm. of water. The blood chemistry was normal.

*Autopsy.*—A large tumor, the size of a small orange, extended caudally from the rostral end of the anterior fossa to the sella turcica, compressing the optic nerves, the optic chiasm, the olfactory tracts and the floor of the third ventricle (fig. 10). The structures on the inferior surface of the brain, from the tip of the frontal pole to the peduncles, including the gyrus cingulus, were distorted and compressed. The tumor did not invade the sella turcica but compressed the entire hypothalamus. Most of the hypothalamic nerve cells showed chromatolysis, shrinkage, severe nerve cell changes of Nissl and loss of pigment granules. The ventricular system did not show significant changes.

*Comment.*—This case could be placed with the cases of hypothalamic lesions were it not that some of the cortical convolutions, especially the orbital gyrus and the gyrus cingulus, were also compressed. It is doubtful whether the pituitary played any role in the causation of somnolence since the sella turcica was not invaded. There was no evidence of increased intracranial pressure.

CASE 23.—*Adenoma of the pituitary gland, with compression of the hypothalamus and the temporo-orbital convolutions; invasion of the hippocampus. Lethargy. Increased intracranial pressure.*

A. G., a man aged 48, complained of loss of libido. A diagnosis of tumor of the pituitary was made. After operation, there appeared visual hallucinations, blindness and drowsiness.

Examination disclosed a blood pressure of 90 systolic and 50 diastolic; small testicles; pale, soft skin; absence of hair on the breast and in the axilla and sparse pubic hair, and amaurosis, with bilateral atrophy of the optic nerve. There were frequent convulsive seizures. The patient was lethargic but could be aroused. Later, confusion and negativism appeared.

*Laboratory Data.*—The urine was normal. The blood urea nitrogen measured 5.6 mg. and the sugar 85 mg. per hundred cubic centimeters. The spinal fluid contained 9 cells per cubic millimeter and 60 mg. of protein per hundred cubic centimeters, with a negative Pandy reaction and an initial pressure of 60 mm.

*Autopsy.*—A large adenoma of the pituitary was situated between and compressed the temporal lobes,

the orbital convolutions and the hypothalamus (fig. 11). A small nodule invaded the left hippocampus (fig. 11). All the hypothalamic nerve cells showed pathologic changes.

*Comment.*—This patient's drowsiness was the result of compression of the hypothalamus, although the effects of cortical involvement cannot be excluded.

CASE 24.—*Suprasellar meningioma, compressing the orbital and cingular gyri and the hypothalamus. Somnolence. Increased intracranial tension.*

S. R., a woman aged 61, when examined showed drowsiness and stupor, from which she could be aroused, pyramidal tract signs on the left, diminution of smell on the right, bilateral papilledema and mental changes. There were no endocrine disturbances except for myxedema. At operation a large meningioma was removed from the right olfactory groove. A spinal tap was not done.

Fig. 11 (case 23).—Adenoma of the pituitary compressing the hypothalamus. Notice the nodule in the left hippocampus.

*Autopsy.*—A tumor originating from the sella turcica compressed the olfactory nerves, the orbital and cingular gyri, the optic nerves, chiasm and tract and the hypothalamus. The sella turcica was eroded but not invaded by the tumor. The entire ventricular system was dilated. The nerve cells throughout the hypothalamus were diminished in number and showed chromatolysis, severe cell changes and loss of iron pigment.

*Comment.*—The somnolence in this case was undoubtedly caused by the pathologic changes in the hypothalamus, secondary to compression. Destruction of cerebral cortex may have been a contributing factor, since some of the convolutions, such as the gyrus cingulus, were compressed.

CASE 25.—*Suprasellar meningioma extending into the anterior and middle fossa, probably compressing the hypothalamus. Somnolence and parkinsonism. Increased intracranial tension.*

P. C., a woman aged 49, had a history of increasing frontal and occipital headaches and fainting spells, followed by changes in personality, such as belligerence, irritability and forgetfulness.

*Neurologic Examination.*—The patient was obese, with a masklike facies and drooling of saliva. She yawned continuously and was drowsy, but could be awakened. The pupils were irregular, the right being larger than the left, and both reacted sluggishly to light. There was bilateral papilledema.

*Laboratory Data.*—The blood chemistry was normal. Spinal tap disclosed an initial pressure of 280 mm. The fluid was clear and contained 3 cells per cubic millimeter, and the total protein measured 46 mg. per hundred cubic centimeters.

*Course.*—With dehydration the patient became somewhat more alert. Craniotomy was performed in the right frontal region, and a meningioma was found attached to the right middle meningeal artery, extending along the base in the frontal fossa and the anterior portion of the middle fossa. It compressed the frontal, orbital and cingular convolutions and the floor of the third ventricle.

*Comment.*—Although the brain was not examined at autopsy, the tumor, which was situated

on the inferior surface of the frontal convolutions and extended into the middle fossa, most likely compressed the basal ganglia and the hypothalamus, thus causing the parkinsonian features and somnolence. The role played by the cortical compression, especially the gyrus cingulus, cannot be ruled out.

## GENERAL COMMENT

In a previous communication concerned with a series of pure cortical lesions, we [1] expressed the opinion that some fibers for the control of sleep may originate in the cerebral cortex, especially the hippocampal, angular, frontal, premotor and temporal convolutions. Bard's [2] experiments on sham rage indicated that the hypothalamus is to some degree under the control of the cerebral cortex. Spiegel [3] postulated the existence of a primitive center of consciousness in the thalamus, which transmits impulses to the higher centers of consciousness located in the cerebral cortex. The cortex, in its turn, can also influence the thalamus, either in an excitatory or in an inhibitory manner. Spiegel also expressed the opinion that corticofugal impulses to autonomic structures may be conducted, at least partly, by fibers joining the pyramidal system and partly by extrapyramidal fibers from areas 3, 4, 5 and 6. Lucksch,[4] Marburg [5] and others stated that both the hypothalamus and the neighboring portions of the mesencephalon and thalamus, though each center is concerned with sleep, are subject to the control of the cerebral cortex. Brailovsky [6] expressed the opinion that sleep is governed by a complex corticosubcortical mechanism, starting with cortical inhibition. Salmon [7] stated the belief that three structures—the cortex, the hypothalamus and the hypophysis—are of importance in the regulation of sleep.

Keeser and Keeser,[8] on the basis of their studies on barbiturates, concluded that the diencephalon was the least important center of sleep and the cerebral cortex the most important. Meyer [9] stated the belief that a change in the condition of the entire cerebral cortex, as well as the subcortical region, is involved in the production of sleep. Among observers who have denied the existence of a discrete sleep center are Salkind,[10] Nachmansohn,[11] Altschuler [12] and Spadolini.[13]

On the basis of observations in this series of cases and those of other investigators and of some of the evidence derived from neuroanatomic and neurophysiologic studies, the following afferent and efferent connections concerned with the sleep mechanism can be postulated:

1. The medial forebrain bundle (part of the hippocampohypothalamic tract), running between the ventromedial olfactory correlation areas of the cortex and the preoptic and hypothalamic areas. There is some evidence for the passage of a septohypothalamic tract via this bundle.

2. Corticohypothalamic fibers, via the fornix, arising in the hippocampus and ending in the medial and lateral mamillary nuclei and in the adjacent rostral portion of the tuber cinereum. Papez [14] stated that the fornix is an important link in a circuit controlling the mechanism of emotion.

3. Inferior thalamic peduncle. Fibers connecting the cortex and the hypothalamus via this peduncle probably originate in the frontal, temporal and hippocampal convolutions.

4. Hypothalamocortical fibers. Such connections have not been demonstrated, but their existence is probable.

2. Bard, P.: A Diencephalic Mechanism for the Expression of Rage with Special Reference to the Sympathetic Nervous System, Am. J. Physiol. **84**:490, 1928.

3. Spiegel, E. A.: Bemerkungen zur Theorie des Bewusstseins und zur Schlafproblem, Ztschr. f. d. ges. exper. Med. **55**:183, 1927; Die Zentren des autonomen Nervensystems, Berlin, Julius Springer, 1928; The Centers of the Vegetative Nervous System, Bull. Johns Hopkins Hosp. **50**:237, 1932.

4. Lucksch, F.: Ueber das Schlafzentrum, Zentralbl. f. d. ges. Neurol. u. Psychiat. **37**:194, 1924; Ztschr. f. d. ges. Neurol. u. Psychiat. **93**:83, 1924.

5. Marburg, O.: Schlaftheorien und Hirnrindenfunction, Wien. klin. Wchnschr. **39**:1076, 1926.

6. Brailovsky, V.: Ueber die pathologische Schläfrigkeit und das Schlafzentrum, Ztschr. f. d. ges. Neurol. u. Psychiat. **100**:272, 1926.

7. Salmon, A.: Le rôle de corrélations cortico-diencéphaliques et diencéphalo-hypophysaires dans la régulations de la veille et du sommeil, Presse méd. **45**: 509, 1937.

8. Keeser, E., and Keeser, J.: Ueber die Lokalisation des Veronals, der Phenyläthyl- und Diallylbarbitursäure im Gehirn, Arch. f. exper. Path. u. Pharmakol. **125**: 251, 1927.

9. Meyer, E.: Ueber organische Nervenerkrankungen im Gefolge von Grippe, Arch. f. Psychiat. **62**:598, 1921.

10. Salkind, E.: Zur Pathogenese des Schlafes nach Beobachtungen bei der epidemischen Encephalitis, Sovet. psikonevrol. **1**:32, 1925; abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **43**:533, 1926.

11. Nachmansohn, D.: Zur Frage des Schlafzentrums: Eine Betrachtung der Theorien über Entstehung des Schlafes, Ztschr. f. d. ges. Neurol. u. Psychiat. **107**: 342, 1927.

12. Altschuler, I. M.: Sleep and Epidemic Encephalitis, J. Neurol. & Psychopath. **9**:222, 1929.

13. Spadolini, N.: Alcune considerazioni sulla fisiologia e fisiopatologia del sonno, Note e riv. di psichiat. **55**:283, 1930.

14. Papez, J. W.: A Proposed Mechanism of Emotion, Arch. Neurol. & Psychiat. **38**:725 (Oct.) 1937.

In 21 of the 25 cases belonging to this group (table), the lesion was neoplastic, with a single tumor in 15 cases and multiplied tumors in 6 cases. Of the entire series of cases of tumor, metastatic neoplasm was present in 5, a suprasellar meningioma in 3 and an adenoma of the pituitary gland in 1. Of the 4 cases in which the lesion was non-neoplastic, a cerebral abscess was present in 1, encephalitis lethargica in 1, diffuse syphilitic disease in 1 and vascular disease in 1. The hypothalamus was compressed and showed pathologic changes in the nerve cells in 16 cases. In 2 cases (5 and 15), the hypothalamus was compressed without changes in the nerve cells. In 4 other cases the hypothalamus was actually invaded, while in 1 case there was partial destruction of the hypothalamus. In about

*Summary of Observations in 25 Cases of Disturbances in Sleep with Corticodiencephalic Lesions*

| Lesion | No. of Cases |
|---|---|
| Neoplasms | |
| Single | 15 |
| Multiple | 6 |
| Abscess of brain | 1 |
| Encephalitis lethargica | 1 |
| Diffuse syphilis of central nervous system | 1 |
| Diffuse vascular lesions | 1 |
| Compression of hypothalamus | |
| With changes in nerve cells | 16 |
| Without changes in nerve cells | 2 |
| Invasion of hypothalamus | 4 |
| Partial destruction of hypothalamus | 1 |
| Evidence of increased intracranial pressure | 18 |
| Ocular manifestations | 4 |
| Disturbances of endocrine glands | 3 |
| Myxedema | 1 |
| Obesity | 1 |
| Deviations in temperature (hypothermia) | 4 |
| Insomnia, later followed by somnolence | 1 |

16 cases, in addition to compression or invasion of the hypothalamus, there was compression (cases 7, 12, 14, 15 and 16) or invasion (cases 1, 2, 3, 4, 5, 6, 8, 9, 10, 13 and 17) of the basal ganglia. The possibility that the striohypothalamic pathways played a role in the disturbance of the sleep mechanism in these cases cannot be entirely excluded. In 3 of the cases of neoplasm the tumor was situated in the suprasellar region. These cases were placed in the category of corticodiencephalic lesions because the hypothalamus or its pathways and part of the orbital convolutions and the cingular gyri were compressed or involved.

The interference with the circulation of cerebrospinal fluid, as evidenced by increased intracranial pressure, was greater in this series than in the cases of pure cortical lesions previously reported,[1] being present in 18 cases. The intracranial pressure was normal in 7 cases of the present series (3, 9, 10, 11, 14, 16 and 22). In 4 of these cases (3, 9, 10 and 11) the lesion was non-neoplastic and in 3 (14, 16 and 22) a tumor. The high incidence of increased intracranial pressure in the cases of corticodiencephalic lesions is to be expected, since in most of these cases the neoplasm compressed the ventricular system. It is doubtful whether increased intracranial pressure played a role in the causation of sleep disturbance.

Ocular manifestations, in the form of diplopia, ptosis, weakness of ocular movements and impairment in conjugate deviation, were present in 4 cases (16, 18, 21 and 25). Very slight endocrine disturbances were found in 3 cases (23, 24 and 25), and in these cases the tumors were situated in or in the vicinity of the sella turcica. In 1 of the cases of suprasellar meningioma there was myxedema and in 1 obesity. Slight deviations in temperature from the normal in the form of hypothermia were present in 4 cases (1, 10, 12 and 22). Insomnia, later followed by somnolence, was found in 1 case (21).

Pathologic sleep as the result of neoplasms which arise in the cortex and invade or compress the hypothalamus has been reported on by other authors. The cases of cerebral trauma with hypersomnia, as reported by a number of observers (Zingerle[15]; Urechia and Bumbacescu[16]), may also belong to this category, since simultaneous lesions were probably present in the cortex and hypothalamus. Cases of tumors near the hypothalamus, compressing it or its corticohypothalamic pathways, possibly belong to the same group. Warren and Tilney[17]; Francioni[18]; Souques, Baruk and Bertrand[19]; Francois and Vernier[20]; Bailey[21]; Wodoginskaja,[22]

15. Zingerle, H.: Ueber einem bei Gehirnkranken künstlich auslösbaren pathologischen Schlafzustand, Klin. Wchnschr. **11**:2143, 1932.

16. Urechia, C. I., and Bumbacescu, M.: Sur quelques cas de troubles du sommeil, Arch. internat. de neurol. **52**:107, 1933.

17. Warren, L. F., and Tilney, F.: Tumor of the Pineal Body with Invasion of the Midbrain, Thalamus, Hypothalamus and Pituitary Body, J. Nerv. & Ment. Dis. **45**:74, 1917.

18. Francioni, C.: Sindromi mesencefaliche con manifestazioni di sonno pathologico, Riv. di clin. pediat. **15**:505, 1917.

19. Souques, A.; Baruk, H., and Bertrand, I.: Tumeur de l'infundibulum avec lethargie isolée, Rev. neurol. **1**:532, 1926.

20. Francois, H., and Vernier, L.: Etudes anatomoclinique d'un cas de tumeur du IIIe ventricule cérébral, Rev. neurol. **35**:921, 1919.

21. Bailey, P.: Some Unusual Tumors of the Third Ventricle, Arch. Neurol. & Psychiat. **20**:1398 (Dec.) 1928.

22. Wodoginskaja, S.: Zur Störung des Schlafes bei Gehirngeschwulsten, Sovet. nevropat. i psychiat. **5**: 2069, 1936; abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **86**:394, 1937.

and others described somnolence in cases of tumors in the vicinity of and compressing the hypothalamic region.

## SUMMARY AND CONCLUSION

In 25 cases of pathologic sleep, there was involvement of the corticodiencephalic structures. The hypothalamus was compressed in 16 cases, and its nerve cells showed pathologic changes in all of these cases. In 4 other cases there was actual invasion of the hypothalamus, while in 1 case there was partial destruction of the hypothalamus. In 2 cases the hypothalamus was compressed without changes in its nerve cells. In 2 other cases there was no compression of the hypothalamus or changes in its nerve cells. In 16 cases, in addition to compression or invasion of the hypothalamus, there was compression or invasion of the basal ganglia with implication of the striohypothalamic pathways. Three cases in which tumors occurred in the suprasellar region were placed in this group because the hypothalamus or its pathways and part of the orbital convolutions and cingular gyri were implicated.

Increased intracranial pressure was present in 18 cases and absent in 7 cases. A high incidence of increased intracranial pressure in this group should be expected, as in most of these cases the neoplasm encroached on the ventricular system.

Ocular manifestations, in the form of diplopia, ptosis, weakness of ocular movements and impairment in conjugate deviation, were present in 4 cases. Slight endocrine disturbances were present in 3 cases, and in these the tumor was situated either within or in the vicinity of the sella turcica. Slight deviations in temperature in the form of hypothermia were present in 4 cases.

From this series of cases of corticodiencephalic lesions, it may be assumed that some fibers for the control of sleep originate in the cortex and reach the hypothalamus via (1) the median forebrain bundle, (2) the fornix and (3) the inferior thalamic peduncle.

1155 Park Avenue.

Montefiore Hospital for Chronic Diseases.

# MULTIPLICITY OF REPRESENTATION VERSUS PUNCTATE LOCALIZATION IN THE MOTOR CORTEX

## AN EXPERIMENTAL INVESTIGATION

J. P. MURPHY, M.D., AND E. GELLHORN, M.D., PH.D.
MINNEAPOLIS

During the course of investigations of cortical motor function under the influence of pain impulses originating in the muscles (Gellhorn and Thompson [1]) and of afferent impulses from the hypothalamus (Murphy and Gellhorn [2]) it was observed that stimulation of a discrete focus with condenser discharges at threshold and suprathreshold intensities led to the production of multiple movements instead of isolated muscular contractions restricted to a small bodily subdivision, which have been described repeatedly. On the basis of these observations, it was decided to reinvestigate the question of multiplicity of motor representation versus punctate localization.[3] Experiments conducted in this study and their interpretation are the subject of the presentation which follows.

A vast and detailed literature concerning motor cortical function has accumulated in the seventy-five years since Fritsch and Hitzig's [4] epoch-making discovery of the electrical excitability of this part of the brain. The communications of Fritsch and Hitzig and of Ferrier [5] about the results of electrical stimulation of motor areas began a train of increasingly painstaking analyses of motor cortical representation, the ultimate goal of which seemed to be definitive assignment of each single muscular effector to a segregated locus in the excitable gray mantle. Physiologic dissection of the motor mosaic may thus be said to have culminated in the studies of Sherrington and Grünbaum [6] on anthropoids and of the Vogts [7] and Hines [8] on monkeys. Garol [9] published similar investigations on the motor cortex of the cat. In the face of such well documented and extensive delimitations of function of the motor cortex, accompanied with carefully drawn pictorial sketches of the results obtained, it would seem, at first thought, somewhat superfluous to add yet another series of observations and maps to the abundant cartography of the motor areas in animals. However, a slight change in method based on a fundamental shift in the point of view made a reinvestigation of the function of the motor cortex imperative.

The spur to further analysis of localization of motor function in the cortex led toward as minute parceling of the cortex into units as possible. This has resulted today in such widespread acceptance of the motor cortex as a repository of the functions of individual muscles and even parts of muscles (Fulton [10]) that it has been likened in operation to the keyboard of a piano (Erickson,[11] Penfield and Boldrey [12]), an opinion

Aided by a grant from the National Foundation for Infantile Paralysis, Inc.

From the Laboratory of Neurophysiology, Department of Physiology, University of Minnesota.

1. Gellhorn, E., and Thompson, L.: The Influence of Muscle Pain on Cortically Induced Movements, Am. J. Physiol. **142**:231-239, 1944.

2. Murphy, J. P., and Gellhorn, E.: Hypothalamic Facilitation of the Motor Cortex, Proc. Soc. Exper. Biol. & Med. **58**:114-116, 1945.

3. Sherrington, C. S.: Selected Writings of Sir Charles Sherrington, edited by D. Denny-Brown, New York, Paul B. Hoeber, Inc., 1940.

4. Fritsch, G., and Hitzig, E.: Ueber die elektrische Erregbarkeit des Grosshirns, Arch. f. Anat., Physiol. u. wissensch. Med. **37**:300-332, 1870.

5. Ferrier, D.: The Functions of the Brain, New York, G. P. Putnam's Sons, 1886.

6. Sherrington, C. S., and Grünbaum, A. S. F.: Localization in the Motor Cerebral Cortex of the Anthropoids, Tr. Path. Soc. London **53**:127-136, 1902.

7. Vogt, C., and Vogt, O.: Zur Kenntnis der elektrisch erregbaren Hirnrindengebiete bei den Säugetieren, J. f. Psychol. u. Neurol. (supp.) **8**:277-456, 1907; Allgemeinere Ergebnisse unserer Hirnforschung, ibid. **25**:277-462, 1919.

8. Hines, M.: Movements Elicited from Precentral Gyrus of Adult Chimpanzees by Stimulation with Sine Wave Currents, J. Neurophysiol. **3**:442-465, 1940.

9. Garol, H.: The Motor Cortex of the Cat, J. Neuropath. & Exper. Neurol. **1**:139-145, 1942.

10. Fulton, J. F.: (*a*) Somatic and Autonomic Functions of the Cerebral Cortex in Ape and Man (Ludvig Hektoen Lecture), Proc. Inst. Med. Chicago **11**:21-42, 1936; (*b*) Physiology of the Nervous System, New York, Oxford University Press, 1938, chap. 20.

11. Erickson, T. C.: Electrical Excitability in Man, in Bucy, P. C.: The Precentral Motor Cortex, Illinois Monographs in the Medical Sciences, Urbana, Ill., University of Illinois Press, 1944, vol. 4, chap. 13, pp. 343-352.

12. Penfield, W., and Boldrey, E.: Somatic Motor and Sensory Representation in the Cerebral Cortex of

based not only on the results of animal experimentation but on observations made during stimulation of the human precentral gyrus (Penfield and Boldrey,[12] Foerster [13]).

*Pari passu,* while discrete and topical functional assignment proceeded apace, abetted by cytoarchitectural expansions, statements found their way into the rapidly accumulating body of knowledge concerning the motor area which expressed a point of view at variance with that of the "punctate" localizers. The supporters of the contrary school of thought—that cortical representation is that of movements, not of muscles, and is several and overlapping rather than single and exclusive—have been found largely in the field of clinical neurology and neurologic surgery (notably Jackson,[14] Horsley [15] and Walshe [16]). This point of view seems to be supported by occasional observations reported in papers the primary aim of which was the foundation and elaboration of the mosaic theory (Beevor and Horsley,[17] Sherrington,[3] Hines,[18] Kennard [19]). That, in addition, the peripheral response to liminal stimulation of the motor cortex (contraction of single muscles or parts of muscles) is far removed from the cortical action underlying voluntary movement goes without saying and is pointed out by even the most firm adherents of the hypothesis of punctate localization (Fulton [10b]).

The important question would seem to be: Should experimental investigation of the function of the motor cortex be confined to the obtaining of the barest discernible muscular responses with the weakest possible electrical currents—"sampling" the cortex, as it were—or should the aim be to evoke, by appropriate stimulation, the full potentialities inherent in the gray matter of the motor area? We believe that the latter point of view is the more defensible, not only because such attempts to reveal cortical functions in their totality would seem to be less artificial and more physiologic, but because it does more to explain clinical observations, particularly those on recovery of function in animals and man after removal of portions or of all of the motor cortex (Horsley,[15] Sherrington and Grünbaum,[6] Foerster,[20] Dusser de Barenne,[21] Hines,[18] Kennard [22] and Bucy [23]).

In keeping with this design the following investigation was undertaken, the aim being to evoke as much as possible rather than as little as possible by stimulation of discrete points on the surface of the motor cortex of animals and then to determine whether or not the results obtained were the expression of purely local activity.

Before methods of investigation and observations are recorded, the most important conditions of our experiments and their limitations should be outlined. First, by "as much as possible" in the preceding paragraph is not meant the production of convulsions. The strength of stimulation, employed in a manner to be described, was purposely suprathreshold in character and ranged from 2.5 to 11 volts. When voltages employed proved to be too high and resulted in convulsions, the corresponding observations were discarded from the series. Next, whereas the recording of combinations of movements was the aim of the experiments, the relationship of these movements to each other in time, so conscientiously recorded by Beevor and Horsley [17] and Hines,[8] was not noted as a rule, for we did not believe such observations to be rele-

Man as Studied by Electrical Stimulation, Brain **60**: 389-443, 1937.

13. Foerster, O.: The Cerebral Cortex in Man, Lancet **2**:309-312, 1931.

14. Jackson, J. H.: Selected Writings of John Hughlings Jackson, edited by J. Taylor, London, Hodder & Stoughton, Ltd., 1931.

15. Horsley, V.: The Function of the So-Called Motor Area of the Brain (The Linacre Lecture), Brit. M. J. **2**:121-132, 1909.

16. Walshe, F. M. R.: The Giant Cells of Betz: The Motor Cortex and the Pyramidal Tract; a Critical Review, Brain **65**:409-461, 1942.

17. Beevor, C. E., and Horsley, V.: A Minute Analysis (Experimental) of the Various Movements Produced by Stimulating in the Monkey Different Regions of the Cortical Centre for the Upper Limb, as Defined by Professor Ferrier, Phil. Tr. Roy. Soc., London, s. B **178**:153-166, 1877.

18. Hines, M.: Significance of the Precentral Motor Cortex, in Bucy, P. C.: The Precentral Cortex, Illinois Monographs in the Medical Sciences, Urbana, Ill., University of Illinois Press, 1944, vol. 4, chap. 18, pp. 459-494.

19. Kennard, M. A.: Somatic Functions, in Bucy, P. C.: The Precentral Motor Cortex, Illinois Monographs in the Medical Sciences, Urbana, Ill., University of Illinois Press, 1944, vol. 4, chap. 9, pp. 243-276.

20. Foerster, O., in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 6.

21. Dusser de Barenne, J. G.: "Corticalization" of Function and Functional Localization in the Cerebral Cortex, Arch. Neurol. & Psychiat. **30**:884-901 (Oct.) 1933.

22. Kennard, M. A.: (*a*) Age and Other Factors in Motor Recovery from Precentral Lesions in Monkeys, Am. J. Physiol. **115**:138-146, 1936; (*b*) Relation of Age to Motor Impairment in Man and in Subhuman Primates, Arch. Neurol. & Psychiat. **44**:377-397 (Aug.) 1940. (*c*) Kennard, M. A., and McCulloch, W. S.: Motor Response to Stimulation of Cerebral Cortex in Absence of Areas 4 and 6 (Macaca Mulatta), J. Neurophysiol. **6**:181-189, 1943.

23. Bucy, P. C.: Effects of Extirpation in Man, in The Precentral Motor Cortex, Illinois Monographs in the Medical Sciences, Urbana, Ill., University of Illinois Press, 1944, vol. 4, chap. 14, pp. 353-395.

vant to the particular problem under study. Also, in the charting of cortical areas from which movements were obtained, the relative magnitude of such movements from point to point is not indicated in the figures which follow. This, again, appeared to be a side issue. Lastly, the observations were confined to movements of the striated muscles of the face and extremities.

The true purpose, in fine, of this study was to investigate experimentally the principle of the multiple representation of movements in the motor cortex insisted on by Jackson [14] and reiterated by Walshe.[24]. We did not, and do not mean to, deny the validity of previous investigations which have had as their intent the revelation of discrete and exclusive muscular foci in the gray mantle. We do mean, however, to shift emphasis from isolated cortical representation to more inclusive cortical function.

The reason for employing members of three animal species (rabbit, cat and monkey) rather than confining attention to the highest of the three was a desire to see whether or not the results obtained under our experimental conditions were correlated with the principle of progressive encephalization (von Monakow,[25] Dusser de Barenne,[21] Fulton,[10b] Sherrington [3]). This was, indeed, found to be the case, but to a lesser degree than expected. The broad principle of multiple representation has been found to be maintained throughout this restricted arc of the phylogenetic hierarchy.

## METHODS

Four rabbits, 7 cats and 6 monkeys were employed as experimental animals. The monkeys (Macacus rhesus) were adolescent and in good health, as evidenced by their life in confinement of over one year. An injection of 0.45 cc. per kilogram of body weight of a solution containing 0.1 Gm. dial and 0.4 Gm. ethyl carbamate per cubic centimeter was given intraperitoneally in all species. Inasmuch as the investigations in the monkey were confined to the precentral and postcentral gyri, reported depression of the premotor cortex by this narcotic (Fulton and associates [26]) was not considered important. Administration of ether by inhalation was frequently added during the exposure of the cerebral hemispheres but was discontinued during the period of stimulation.

The head was rigidly held in the frame of the Horsley-Clarke instrument, to which electrode holders provided with rack and pinion were attached. This arrangement, precluding careful observation of movements of the head or neck, did not militate against the original plan of experiment. The body was supported in such a manner that the head was lower than the caudal region, to counteract the known hypotensive effects of dial (Fulton and associates [26]), and that the extremities could move freely.

Unilateral or bilateral craniectomy—the latter in stages—was undertaken by the usual methods, particular attention being paid to careful hemostasis to prevent subarachnoid hemorrhage. In the cat, this meant careful thermocoagulation of fine, almost invisible vessels running from the surface of the cortex to the cerebral dura, the presence of which is not noted in previous descriptions of the intracranial anatomy of this animal. To insure adequate exploration of all of the lateral and under surfaces of the cerebral hemisphere in the cat, the eye was either removed or retracted inferiorly by the placement of sutures in the superior rectus muscle. The latter procedure, while denying as much available area as removal of the eye and orbital tissues, proved much less shocking than the more radical operation. When it was feared that shock had supervened, ephedrine was given and stimulation postponed.

The dura was carefully reflected medially, and vessels entering the superior sagittal sinus were left intact unless their presence interfered too greatly with free exploration, in which case they were coagulated and divided. In instances in which this was necessary adequate drainage of the cortex would seem to have been still maintained.

Such deterrent factors to optimal cortical function as cooling of the brain, drying of the surface and general hypothermia (Sherrington [3] and others) were combated by the placing of lamps, one over the body of the animal and another in close proximity to the exposed hemisphere, and the frequent application of warm Ringer solution to the cortex. Saturated pledgets of cotton were arranged over the area of decompression so as to form a moist chamber. Neither of these procedures resulted in the physical spread of current predicted by other investigators (Garol [9]). As in previous investigations,[27] the cortex was stimulated through bipolar silver electrodes placed 2 to 3 mm. apart with Goodwin's [28] apparatus, which permits independent control of duration, frequency and intensity of condenser discharges.

The frequency of stimuli chosen for almost all stimulations was 90 per second. This is at the upper range of frequencies considered by Hines and Boynton [29] to be most effective during stimulation with sine waves, and in our own hands it has proved to be best suited for the purposes used. Voltages were almost always supraliminal but far below convulsive level. The duration of impulse was 20 milliseconds (Garol [9]); the period of stimulation, ten seconds. Therefore, the conditions were those of primary facili-

24. Walshe, F. M. R.: On the Mode of Representation of Movements in the Motor Cortex, with Special Reference to "Convulsions Beginning Unilaterally" (Jackson), Brain **66**:104-139, 1943.

25. von Monakow, C.: Die Lokalisation im Grosshirn, Wiesbaden, J. F. Bergmann, 1911.

26. Fulton, J. F.; Liddell, E. G. T., and Rioch, D. M.: "Dial" as a Surgical Anesthetic for Neurological Operations, with Observations on the Nature of Its Action, J. Pharmacol. & Exper. Therap. **40**:423-432, 1930.

27. Gellhorn and Thompson.[1] Murphy and Gellhorn.[2]

28. Dusser de Barenne, J. G.; Garol, H. W., and McCulloch, W. S.: The "Motor" Cortex of the Chimpanzee, J. Neurophysiol. **4**:287-303, 1941.

29. Hines, M., and Boynton, E. P.: The Maturation of Excitability in the Precentral Gyrus of the Young Monkey (Macaca Mulatta), Contrib. Embryol. **28**:309-451, 1940.

tation (Bubnoff and Heidenhain,[30] Brown[31] and Adrian[32]). One or two minutes was allowed to elapse between successive stimulations. This time was considered long enough to allow after-effects from previous facilitations to be dispersed and to obviate "secondary facilitation" (Brown,[31c] McCulloch[33]), since constancy of cortical response prevailed under these conditions.

In the rabbit, the cortical area stimulated consisted of all that was responsive, beginning anteriorly and moving posteriorly until silent cortex was encountered. This usually proved to be about one-third the distance from the frontal pole to the torcular Herophili. The far posterior, occipital, area found by Exner[34] to be productive of movements of the foreleg was not included. In the cat, the gyri stimulated included the anterior and posterior sigmoid gyri; the coronal gyrus; the gyrus proreus; the gyrus lateralis; the anterior and middle suprasylvian gyri; the anterior, middle and posterior ectosylvian gyri, and the anterior, middle and posterior sylvian gyri (Winkler and Potter[35]). Exploration in the monkey was confined to the precentral and postcentral gyri and therefore encompassed areas 4q and 4r of McCulloch,[33] area 44 and the posteroinferior tail of area 6, as well as areas 3, 1, 2 and 5. Stimulations in the monkeys were arbitrarily discontinued at what was thought by gross inspection to be the posterior limit of the strip, or suppressor area, of Hines.[18] All of areas 4q and 4r may therefore not have been stimulated in certain instances, but inasmuch as the intent of the investigation was to confirm a principle, and not to evoke all movements wherever possible, this was of small moment.

30. Bubnoff, N., and Heidenhain, R.: On Excitatory and Inhibitory Processes Within the Motor Centers of the Brain, translated by G. von Bonin and W. S. McCulloch, in Bucy, P. C.: The Precentral Motor Cortex, Illinois Monographs in the Medical Sciences, Urbana, Ill., University of Illinois Press, 1944, vol. 4, chap. 7.

31. Brown, T. G.: Studies in the Physiology of the Nervous System: (*a*) XXII. On the Phenomenon of Facilitation; 1. Its Occurrence in Reactions Induced by Stimulation of the "Motor" Cortex of the Cerebrum in Monkeys, Quart. J. Exper. Physiol. **9**:81-99, 1915-1916; (*b*) XXIII. On the Phenomenon of Facilitation: 2. Its Occurrence in Response to Subliminal Cortical Stimuli in Monkeys, ibid. **9**:101-116, 1915-1916; (*c*) XXIV. On the Phenomenon of Facilitation: 3. "Secondary Facilitation" and Its Location in the Cortical Mechanism Itself in Monkeys, ibid. **9**:117-130, 1915-1916; (*d*) XXVII. On the Phenomenon of Facilitation: 6. The Motor Activation of Parts of the Cerebral Cortex Other Than Those in the So-Called "Motor" Area in Monkeys (Excitation of the Post-Central Gyrus), with a Note on the Theory of Cortical Localisation of Function, ibid. **10**:103-143, 1916-1917.

32. Adrian, E. D.: The Spread of Activity in the Cerebral Cortex, J. Physiol. **88**:127-161, 1936.

33. McCulloch, W. S.: Cortico-Cortical Connections, in Bucy, P. C.: The Precentral Motor Cortex, Illinois Monographs in the Medical Sciences, Urbana, Ill., University of Illinois Press, 1944, vol. 14, chap. 8, pp. 211-242.

34. Exner, S.: Zur Kenntniss der motorischen Rindenfelder, Sitzungsb. d. k. Akad. d. Wissensch. Math.-naturw. Cl. **84**:185-190, 1881.

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

In order to decide the part played by physiologic spread of impulse and that by purely local activity at the point stimulated, certain cortical points were isolated by transcerebral section. Typical examples of such experiments are recorded later. In performing these isolations, the intent was to cut through not only the cortex proper but the U fibers, although evidence concerning physiologic spread in he cortex (Adrian,[32] Erickson,[36] Fulton,[37] McCulloch,[33] Rosenblueth and Cannon[38]) indicates intracortical transmission only under conditions of primary facilitation. Isolation was made on all four sides in some experiments and on only three in others in which the tissue posterior to the block segregated surgically was electrically nonresponsive. The depth of incision was checked at autopsy, after fixation of the brain in solution of formaldehyde U. S. P. (1:4). It was found in almost all cases to have been deep enough to interrupt not only intragriseal but possible U fiber conduction pathways. Sketches of these isolated blocks are presented in figures 6, 7 and 8, with respective protocols described in tables 1, 2 and 3. To mitigate the effect of the factor of trauma, stimulation of the isolated block was not undertaken until an interval of ten to thirty minutes had elapsed.

## RESULTS

Figures 1, 2 and 3 present pictorially the results of stimulation under conditions of primary facilitation in individual rabbits, cats and monkeys. Each symbolic line, the significance of which is indicated in the legends, encompasses the area of the excitable cortex which responded to stimulation by a movement through a particular joint to any degree, no discrimination being made with reference to intensities of response.

The principal observation in the investigation which applies to the three species studied may be summarized in the statement that under conditions of primary facilitation, multiple representation of movement is widespread in the motor cortex of the rabbit, cat and monkey. The most common type of multiple representation is that found within large somatotopic divisions (leg, arm, face). As figures 1 to 3 demonstrate, there is considerable overlap of the areas from which movements activating the various joints of the leg or of the arm are elicited, and a similar statement applies to the face and head area. Thus, in figure 2 *A* and *C* show almost complete identity of the boundaries of the cortical areas for movements of the hip, knee and hindfoot in the cat, while in figure 3 *A* and *C* illustrate that in the monkey the cortical areas for movement of the hip, knee, ankle and toes practically coincide, as

36. Erickson, T. C.: Spread of the Epileptic Discharge, Arch. Neurol. & Psychiat. **43**:429-452 (March) 1940.

37. Fulton, J. F.: Paralyses of Cortical Origin, Proc. California Acad. Med. 1933-1934, pp. 1-20; footnote 10 *b*.

38. Rosenblueth, A., and Cannon, W. B.: Cortical Responses to Electrical Stimulation, Am. J. Physiol. **135**:690-741, 1942.

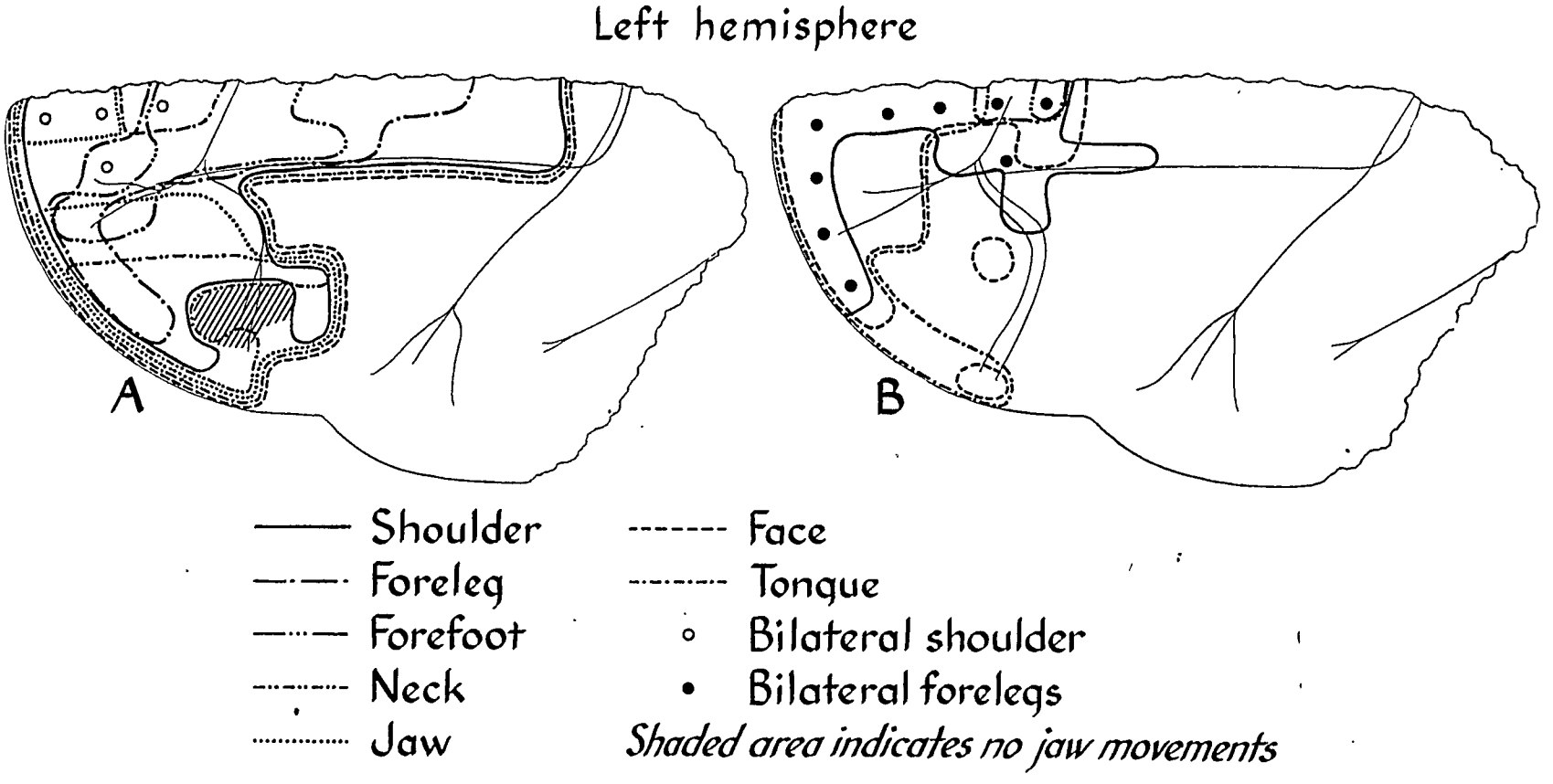



Fig. 1.—Maps of cortical motor response (left hemisphere) in the rabbit (2 animals), summarizing the results of suprathreshold stimulation with condenser discharges under conditions of primary facilitation. Extensive overlap of movements with multiplicity of representation is shown.

Fig. 2.—Maps of cortical motor response (left hemisphere) in the cat (3 animals) under conditions of stimulation similar to those noted for figure 1. In general movements of the hindleg are medial and posterior, and responses of the foreleg and face, anterolateral and posterolateral, respectively, but widespread multiplicity of representation is clearly evident.

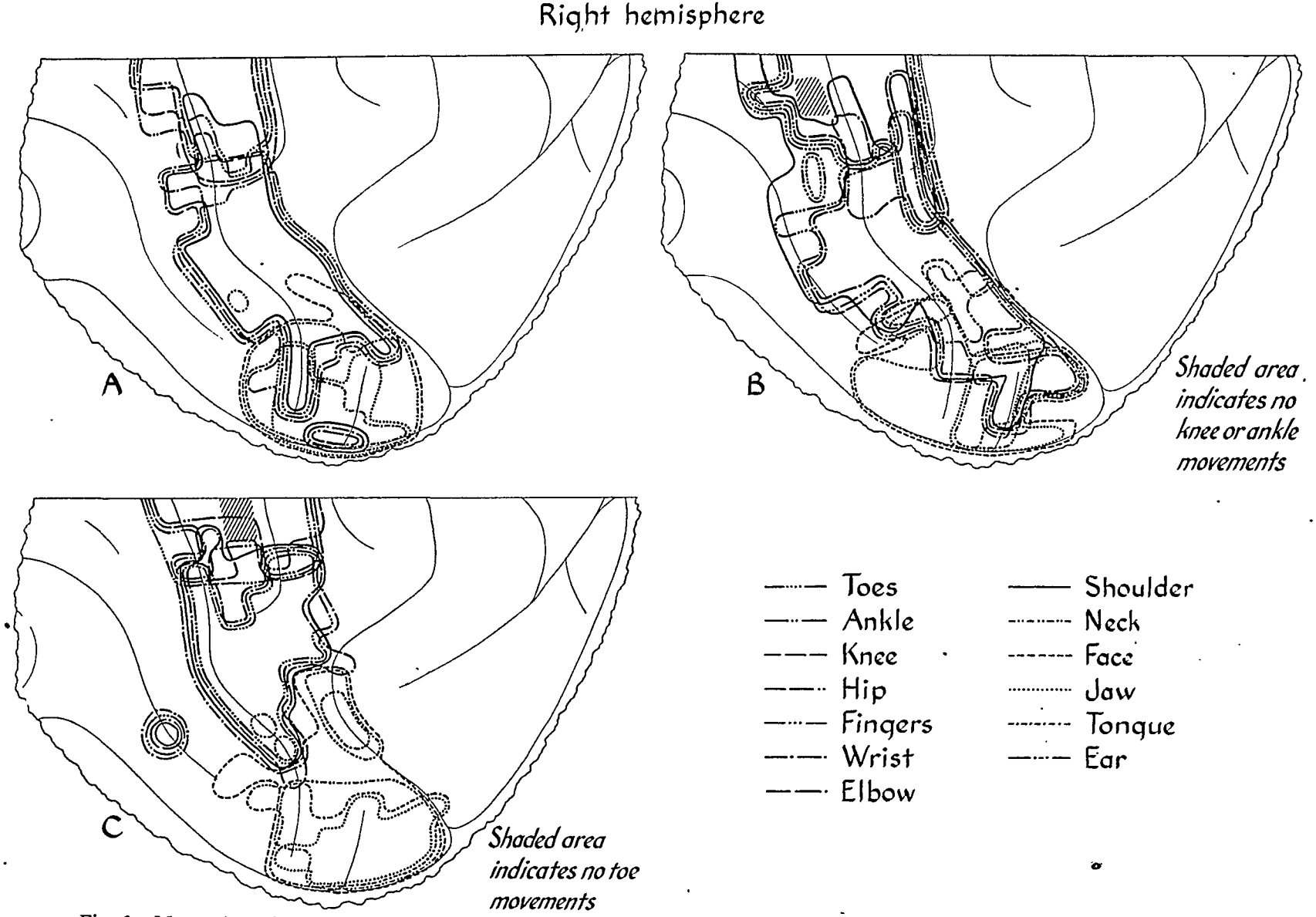



Fig. 3.—Maps of cortical motor response (right hemisphere) in the monkey (3 animals) under conditions of primary facilitation. The three major divisions (areas for the leg, arm and face) are represented in a medial-lateral direction in the precentral and post-central gyri, with less overlap of their borders than in the rabbit and cat. However, extensive multiplicity of representation exists within each of the three areas.

do the boundaries for movements of the shoulder, elbow, wrist and fingers. There is less agreement in the boundaries of cortical areas for the facial muscles, tongue, jaw and ear in the cat and the monkey, although considerable overlap is found here too.

Cortical overlap of two large somatotopic subdivisions, likewise found in all three species, is greatest in the rabbit and least in the monkey. It apparently decreases with progressive encephalization as the phylogenetic scale is ascended. The cortical areas representing movements of the shoulder, face and tongue are almost coextensive in the rabbit (particularly in figure 1 *A*), and considerable overlap of the cortical areas representing movements of the jaw and shoulder also exists. Extensive overlap of the cortical areas for the hindleg and foreleg, as well as those for the foreleg and face, is seen in figure 2 *A* to *C*, but, despite considerable individual differences, there is less overlap of the areas for the face and the foreleg in the cat than was seen in the rabbit. Finally, the large somatotopic divisions coincide least in the monkey (fig. 3 *A* to *C*), but it is worthy of note that the movements activating the various joints of the foreleg could be elicited from a small portion of the area for the hindleg. Such overlap is found more extensively between the face and the foreleg area, although enormous quantitative differences exist in individual animals.

Close inspection of figures 1 to 3 reveals that even in the rabbit there are boundaries beyond which certain movements cannot be obtained despite responsiveness of the gray mantle, and in the monkey these boundaries are more constrictive. In the latter animal the borders more or less correspond to those delimiting the large sensorimotor areas of Dusser de Barenne [39] but are not as sharply exclusive. There is little physiologic correspondence under our experimental conditions to cytoarchitectonic fields (monkey). The maps summarizing these observations in representative examples (figures 1, 2 and 3) are far different from those accepted as indicative of functional localization in the animals investigated.

Inasmuch as punctate or mosaic localization was not our intent, there would be no point in correlating movements represented with individual foci. However, certain features of the results of our stimulations merit individual, but brief description.

1. Most of the experiments, as noted, were conducted with the intensity of stimulation above threshold. Even at threshold, however, and under conditions of primary facilitation, a multiple response was the rule. In only 1 monkey experiment was an isolated muscular contraction, that of the extensor digitorum longus, seen.

2. Although our preoccupation was with movements through joints, a cortical point which, for example, was recorded as representing "wrist" alone was still a point with multiple activities, for wrist movements were not simply flexion or extension; they were "fixation" (cocontraction of extensors and flexors). As might be expected, this was usual when wrist movements were combined with flexion of the fingers, but it was also true when wrist movement was seen alone.

3. Surprisingly—and this is extremely important—the movements most widely represented were not the most peripheral: Following Jackson [14] and Walshe,[24] we had anticipated that the opposite would be true. Such, however, was not the case. As may be seen from a glance at the accompanying maps, movements through proximal joints (shoulder, knee) were at least as widely evoked as were reactions involving more distal joints (paws, fingers, toes), and in some instances even more widely.

4. Although our maps purposely avoid a distinction between the occurrence of a certain movement as a primary or as a secondary movement, several experiments were conducted on cats in order to determine whether or not cortical points which responded first with flexion of the knee, for instance, and, then, as stimulation proceeded, with additional movements had a lower threshold for the knee reaction than had other points from which the knee reaction was obtained secondarily or tertiarily. There was no correlation between the level of threshold for a movement and its primacy of response. Equally of interest is the fact that the accepted "knee" area in the cat, for example (Garol [9]), did not have a lower threshold for knee movements than did more outlying (with reference to Garol's map) regions, and this held true for all other movements. However, a low threshold area was found consistently at the lower, lateral, end of the cruciate sulcus and for about 5 mm. around it in all directions.

5.[40] In many individual stimulations, there was a latency of motor response, referred to in

39. Dusser de Barenne, J. G., and McCulloch, W. S.: Functional Boundaries in the Sensori-Motor Cortex of the Monkey, Proc. Soc. Exper. Biol. & Med. **35**:329-331, 1936. Dusser de Barenne, J. G.: Sensori-Motor Cortex and Optic Thalamus, in Report of Eleventh International Congress of Psychology, Paris, 1937.

40. Paragraphs 5 to 12 refer to incidental observations which seemed worthy of record.

previous communications from this laboratory, of one or more seconds after application of stimulus. This was undoubtedly the expression of "summation time" (Adrian,[32] Cooper and Denny-Brown [41]), and it has been noted to be of similar length—up to 5 or 6 seconds—by others (Clark and Ward'[42]). The length of latency in our hands may have been due to the relatively high frequency of stimulation (Rosenblueth and Cannon [38]). It was particularly obvious in the monkey during stimulation of the parietal and precentral operculums.

6. The movements observed evidenced cocontraction, as well as the reciprocal innervation which Sherrington [3] observed during cortical activity. The degree of cocontraction and its timing in the motor response are to be investigated further by electromyographic studies, but its presence was established beyond doubt by observation and palpation of muscles and by preliminary myograms. This is supportive evidence of the relatively physiologic character of these experiments, for, as noted by Jackson [14] and others,[43] coinnervation is the rule in voluntary movement.

7. Although, owing to rigid fixation of the electrodes and suitable intervals of stimulation, the cortical response was quite constant, it was seen that variations in the intensity of stimulation influence the response not only quantitatively but qualitatively. With near threshold stimulation, movements were often extensor in type, particularly in the monkey. With increase in intensity, flexor movements became predominant. Although no further analysis was attempted, it is realized that this result depends not only on the cortex but on the relative strength of flexor and extensor muscles, as well as on the state of the lower motor neuron (Magnus [44]).

8. The movements observed in the monkey were pseudopurposive in character but were also strangely like dystonic contractions characteristic of choreoathetosis in the human being. Bucy [45] has called attention to the similar appearance of movements elicited by stimulation of the premotor cortex of the macaque. We believe that this applies to the motor cortex proper and may be pertinent to the problem of surgical relief of dystonia by excision of the precentral rather than the premotor cortex in man (Horsley,[11] Bucy [23]).

9. Inhibitory, as well as excitatory, responses were noted in all three species from stimulation of foci not known to be suppressor in character. This inhibitory response was effective on spontaneous activity. It was often obtained with lower intensities than were excitatory effects and indicated the approach of the excitatory threshold. In addition, it was frequently observed that

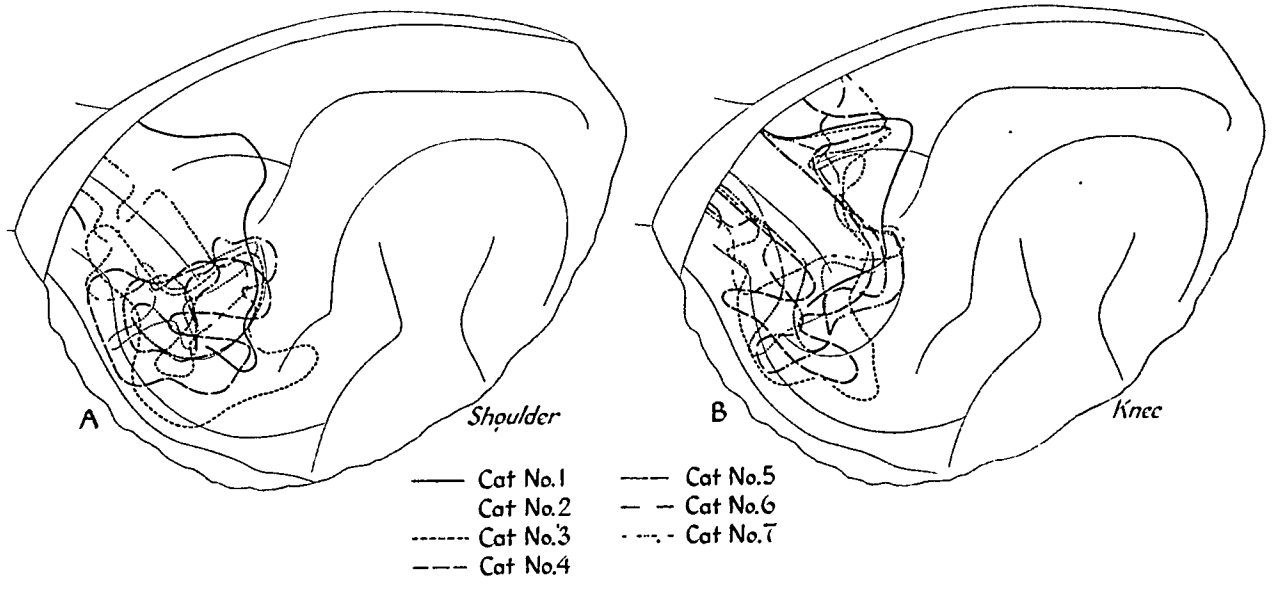



Fig. 4.—Individual variations in cortical representation (left hemisphere) of shoulder and knee movements, respectively, in 7 cats.

41. Cooper, S., and Denny-Brown, D. E.: Responses to Stimulation of the Motor Area of the Cerebral Cortex, Proc. Roy. Soc., London, s. B **102**:222-236, 1927.

42. Clark, S. L., and Ward, J. W.: Electrical Stimulation of the Cortex Cerebri of Cats, Arch. Neurol. & Psychiat. **38**:927-943 (Nov.) 1937.

43. Hathaway, S. R.: An Action Potential Study of Neuromuscular Relations, J. Exper. Psychol. **18**:285-298, 1935.

44. Magnus, R.: Körperstellung, Berlin, Julius Springer, 1924.

45. Bucy, P. C.: The Relation of the Premotor Cortex to Motor Activity, J. Nerv. & Ment. Dis. **79**: 621-630, 1934.

the excitatory effect characteristic of the area stimulated followed the inhibitory action after a latency of one or more seconds.

10. After-discharge was sometimes seen after termination of ten seconds' stimulation in all three species but was not recorded as movement from stimulation. Intensities were usually reduced, and the experiment was repeated. Although not pertaining to our specific problem, it may be mentioned that after-discharge often anticipated the "true" motor response obtained with a slightly higher degree of stimulation. In isolation experiments, section through the anterior lip of the central sulcus did not prevent the appearance of after-discharge. Both of these observations are contrary to the statements of Sapirstein.[46]

11. With suprathreshold but subconvulsive stimuli no movements of the hindlegs or the ear were elicited in the rabbit.

12. "Islands" of limited representation in the midst of fully responsive regions may correspond to the silent zones noted by Sherrington [3] (figs. 1 *A*, 2 *C* and 3 *B* and *C*).

Figures 4 and 5 depict a phenomenon which appears to be the laboratory counterpart of Penfield and Boldrey's [12] observations based on a series of stimulations of human brains. These figures indicate a considerable lack of correspondence from animal to animal of areas responsive with shoulder and knee movements in

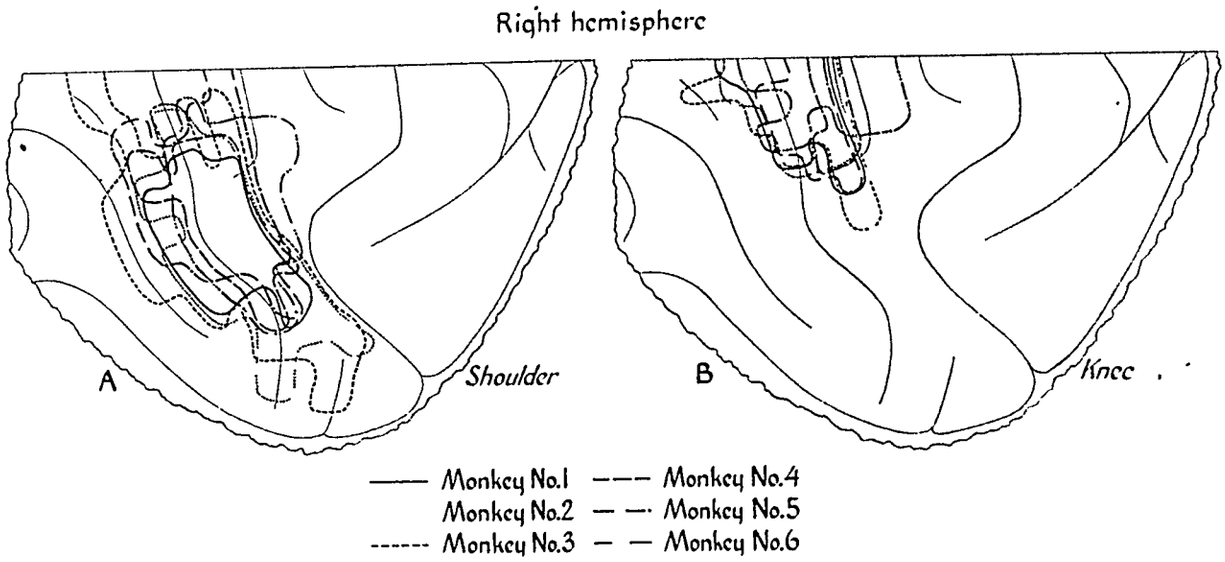



Fig. 5.—Individual variations in cortical representation (right hemisphere) of shoulder and knee movements in 6 monkeys.

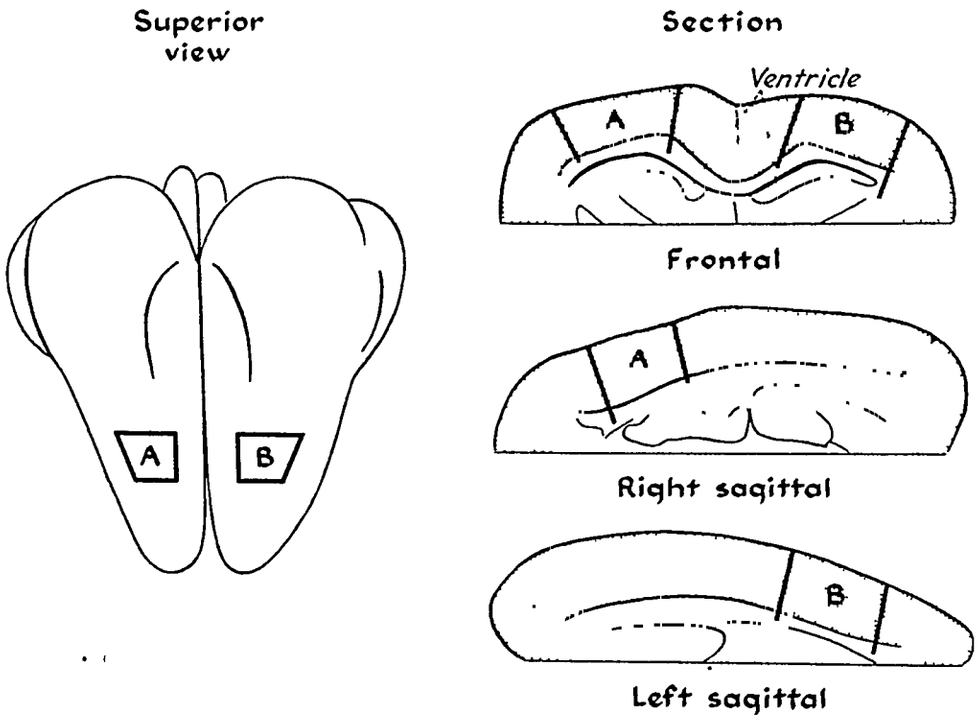



Fig. 6.—Diagrams of isolation of two cortical foci (3 by 5 mm.) in the rabbit. Results of stimulation are recorded in table 1.

46. Sapirstein, M. R.: Characteristics of After-Discharge Following Cortical Stimulation in the Monkey, Arch. Neurol. & Psychiat. **46**:665-675 (Oct.) 1941.

the cat and monkey. Again, individual variation is less extensive in the more "encephalized" monkey but is still present to a measurable degree. Factors to which this discrepancy is accountable are numerous; perhaps most important is the degree of narcotization. Ferrier [5] early recognized the influence of the depth of anesthesia on cortical response, as did Bubnoff and Heidenhain.[30] Clark and Ward,[42] in a remarkable series of experiments on cats, in which they stimulated the cortex in the unanesthetized animal and then compared results with those obtained during varying degrees of anesthesia, noted a considerable discrepancy and attributed this to interference on the part of the anesthetic with processes of facilitation. Neurosurgeons are well aware of the anesthetic depression of the human cortex. The investigations of Derbyshire, Rempel, Forbes and Lambert [47] on the influence of anesthetics on spontaneous cortical potentials are of correlative interest.

Individual cortical variation may also depend on the degree to which narcosis interferes with tonic afferent impulses (e. g., from thalamus and hypothalamus), the facilitatory influence of which has been previously demonstrated.[27]

Another factor to be considered as an explanation of the individual variations in location of responsive areas is that of difference in cerebral topography, emphasized by Sherrington.[3] Breadth of sulci and depth of fissures, exposing more or less cortex to the exciting current, undoubtedly play a significant part in the results obtained by cortical stimulation. Circulatory differences and inherent differences in threshold, extremely difficult of estimation, likewise influence the results.

Also, developmental considerations undoubtedly influence the location of the excitable area. In figure 3 *C* (monkey) the excitable area seemed to have "migrated" anteriorly, the end result being displacement of the strip (area 4-s) forward, leaving responsive cortex in its place.

### ISOLATION EXPERIMENTS

The validity of our thesis, that movements are represented severally rather than singly in the motor cortex, depends on the success of experiments in which the cortical points stimulated were isolated from the surrounding gray matter. These crucial experiments will be reported in detail.

The importance of such cortical isolations to the soundness of our argument was recognized from the start of this investigation, for it is freely admitted that the results depicted in the maps previously referred to might be accountable to (1) physical spread or (2) physiologic spread of the exciting impulse under the conditions of primary facilitation.

Before block segregations of reactive foci were undertaken, the degree of physical spread of current from the electrical field between the two stimulating electrodes was determined. If, as has been claimed (Bubnoff and Heidenhain,[30] Garol [9]), a wet cortical surface is a uniform conductor of electricity in all directions, even with bipolar stimulation, considerable leakage of current should be detectable at a short distance from the electrodes. Cathode ray oscilloscopic records have demonstrated, on the contrary, the falsity of such an assumption and have clearly proved that the electrical field, even with stimulation for ten seconds at relatively high intensities, remains restricted, practically speaking, to the tissue between the electrodes. During stimulation with 11 to 12 volts for the period described (ten seconds) there is a sharp drop in voltage from that found between the electrodes to about 50 per cent of the original value 1 mm. away from the interelectrodal area and to about 25 per cent 2 mm. away. It may be argued that there is still spread of current physically, even though it be of only 50 or 25 per cent of the whole. This is true, but stimulation of the points 1 to 2 mm. distal to the original focus with 50 per cent of the original current caused no response whatever. Therefore, the amount of physical spread under our experimental conditions was negligible and could by no means have accounted for multiplicity of motor response in itself.

The part that physiologic spread of self-propagating neuronal discharges might play is much more important to the solution of the explanation of multiplicity of reaction to cortical stimulation. As first described by Adrian,[32] activation of the deep pyramidal layers in the motor cortex results in a "wave of positivity" which spreads in all directions to points as far as 5 to 8 mm. distant (rabbit). This type of transmission has been seen by Dusser de Barenne and collaborators (McCulloch [33]) during local strychninization of the cortex and is thought to account for the response of broad regions of the cortex to the application of the drug. It is also implicated (Erickson,[36] Rosenblueth and Cannon [38]) in the general epileptic discharge. Therefore, might not physiologic spread under these circumstances account for our results?

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

It was at this point that cortical isolations were undertaken. Inasmuch as Adrian's "wave of positivity" is believed (Dusser de Barenne and McCulloch [39]) to depend on neuronal synapses within the deep layers (large and giant pyramidal cell laminas), simple incision through the gray mantle on all four sides surrounding a cortical focus should be sufficient to eliminate it. However, because it was felt that intergyral U fiber connections (Mettler [48]) might conceivably conduct some sort of propagated impulse, the depth of incision was calculated to extend through the U fiber layer, at the junction between cortex and subcortex.

Segregations of foci were therefore made in animals from each species. Rectangular cortical islands, measuring 5 mm. long by 3 mm. broad, were isolated. The site of the blocks prepared and their gross appearance in two planes at autopsy are shown in figures 6, 7 and 8. Protocols illustrating the retention of multiplicity of response and its intensification by hypothalamic facilitation (Murphy and Gellhorn [2]) after isolation of cortical points are given in tables 1, 2 and 3.

These tables demonstrate beyond question that representation of movements in a single cortical focus does not depend on physiologic spread of generated neuronal impulses into adjacent areas of the cortex but is a function of the "point" directly stimulated.

It might be pointed out that after cortical isolation stronger stimulation was necessary to evoke the control response, or something very close to it, and even that in 1 experiment tabulated (table 2 *C*) the island reacted only with a "trace" response through one joint. However, hypothalamic facilitation now brought out movements of the shoulder and foreleg which had been present before. It should be added that these were true cortical movements and not due to

TABLE 1.—*Cortical Isolations in the Rabbit (fig. 6)* *

| | Intensity (Volts) | Face | Tongue | Jaw | Right Shoulder | Left Shoulder |
|---|---|---|---|---|---|---|
| A. Isolation of Right Frontal Block on Four Sides | | | | | | |
| Control | 11 | + | + | .. | + | + |
| Postisolation | 11 | .. | + | .. | .. | + |
| Postisolation | 17 | ++ | ++ | .. | ++ | ++ |
| B. Isolation of Left Frontal Block on Four Sides | | | | | | |
| Control | 11 | + | + | .. | (+) | ++ |
| Postisolation | 11 | + | ++ | ++ | (+) | ++ |

* In this table, and in tables 2 and 3, the scale of gradation of movements is as follows: (+), trace; +, minimal flexion; ++, moderate flexion; +++, maximal flexion. All stimulations were made for ten seconds at a frequency of 90 per second.

TABLE 2.—*Cortical Isolations in the Cat (fig. 7)*

| | Intensity (Volts) | Shoulder | Elbow | Forefoot | Hip | Knee | Hindfoot |
|---|---|---|---|---|---|---|---|
| A. Isolation of Right Frontal Block on Four Sides | | | | | | | |
| Control | 6.7 | .... | .... | .... | .... | + | + |
| Postisolation | 5.7 | .... | .... | .... | .... | + | + |
| B. Isolation of Right Frontal Block on Three Sides | | | | | | | |
| Control | 6.7 | (+) | .... | .... | +++ | +++ | +++ |
| Postisolation | 11 | (+) | .... | .... | ++ | ++ | ++ |
| Postisolation, hypothalamic facilitation * | 11 | + | ++ | .... | +++ | +++ | +++ |
| C. Isolation of Left Frontal Block on Three Sides | | | | | | | |
| Control | 8.2 | ++ | ++ | ++ | .... | ++ | ++ |
| Postisolation | 11 | .... | (+) | .... | .... | .... | .... |
| Postisolation, hypothalamic facilitation * | 11 | + | ++ | .... | .... | .... | .... |
| D. Isolation of Right Frontal Block on Three Sides (between lines 3 and 4) | | | | | | | |
| Control | 9.75 | .... | .... | .... | .... | ++ | ++ |
| Postisolation | 8.25 | .... | .... | .... | .... | (+) | (+) |
| Postisolation, hypothalamic facilitation * | 8.25 | .... | .... | .... | .... | + | + |

* Simultaneous stimulation of cortex and hypothalamus (mamillary nuclei, inductorium 8 C.D.).

TABLE 3.—*Cortical Isolations in the Monkey (fig. 8)*

| | Intensity (Volts) | Face | Jaw | Neck | Shoulder | Elbow | Wrist | Hip | Knee | Fingers | After-Discharge |
|---|---|---|---|---|---|---|---|---|---|---|---|
| A. Isolation of Block at Midpoint of Precentral Gyrus on Four Sides | | | | | | | | | | | |
| Control | 9.7 | .... | .... | .... | + | + | ++ | .... | ++ | +++ | 30 sec. |
| Postisolation | 11 | .... | .... | .... | + | + | +++ | (+) | ++ | +++ | 32 sec. |
| B. Isolation of Block Below Midpoint of Precentral Gyrus on Four Sides | | | | | | | | | | | |
| Control | 8.25 | .... | .... | .... | ++ | ++ | ++ | .... | .... | +++ | |
| Postisolation | 11 | .... | .... | .... | (+) | (+) | + | .... | .... | ++ | |
| C. Isolation of Block at Foot of Precentral Gyrus on Four Sides | | | | | | | | | | | |
| Control | 8.25 | ++ | (+) | .... | (+) | ++ | +++ | .... | .... | +++ | |
| Postisolation | 11 | +++ | + | + | .... | .... | .... | .... | .... | .... | |

48. Mettler, F. A.: Corticofugal Fiber Connections of the Cortex of Macaca Mulatta: The Frontal Region, J. Comp. Neurol. **61**:509-542, 1935.

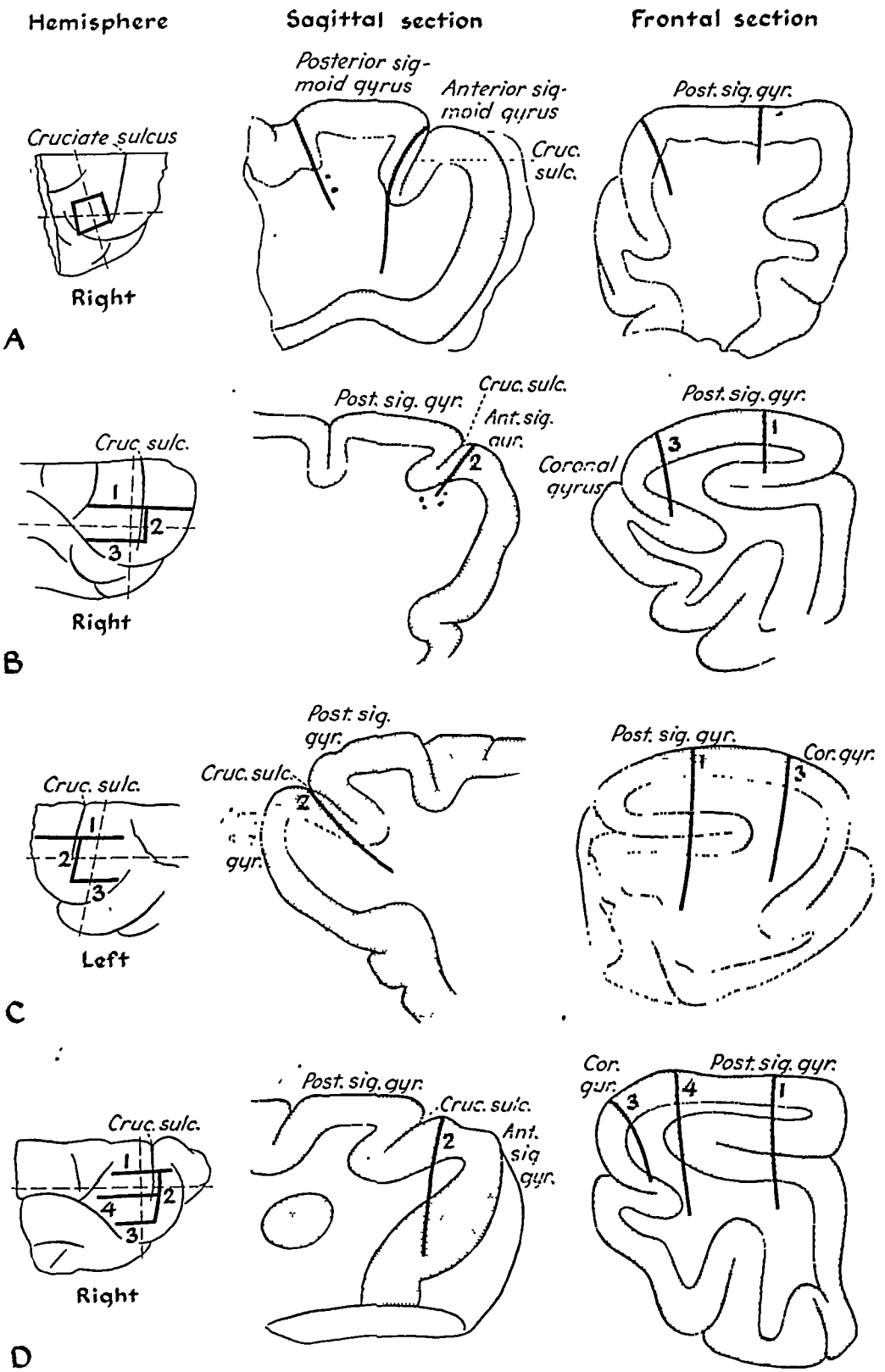



Fig. 7.—Diagrams of isolation of cortical foci (3 by 5 mm.) in 4 cats. Results of stimulation are recorded in table 2. Broken lines through hemispheres correspond to planes of section at autopsy (in *D* the block stimulated is bounded by lines 2, 3 and 4).

activation of the hypothalamus as such (Murphy and Gellhorn [2]).

In some experiments not all the movements were retained after isolation, and in many the movements, while still present, were not as strong as in the control. It is believed that these effects are due to trauma consequent on the surgical procedure because in other experiments listed the postisolation reaction was the counterpart of the control and because the islands prepared were very small (5 mm. long by 3 mm. wide). The deep incisions pictured in figure 6, 7 and 8 necessarily interfered with local blood supply, and there was almost invariably some

## COMMENT

It was one of our purposes in planning the investigation to devise a type of stimulation which would be as nearly physiologic as possible. Investigators who have used brief-acting, threshold currents, usually faradic in type, admit that the situation is highly unphysiologic and the results observed artificial in the sense that they do not resemble voluntary motion at all (Brown [31d] and Kennard [19]). On the other hand, it would seem logical to suppose that volitional initiation of motor activity, a process of some temporal magnitude, involves the setting up of

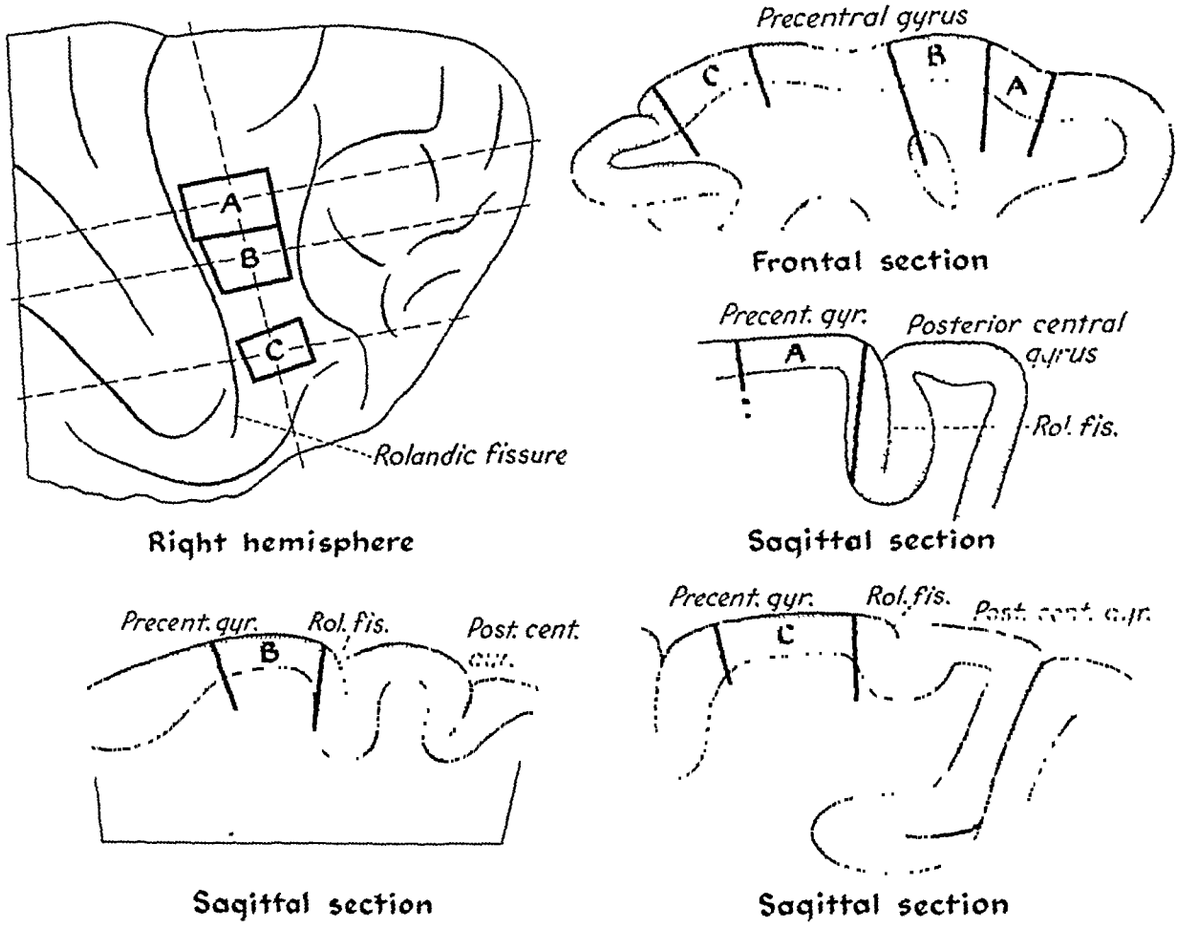



Fig. 8.—Diagrams of isolation of three cortical foci (3 by 5 mm.) in 2 monkeys projected on one diagram. Results of stimulation are recorded in table 3.

blood in the subarachnoid space overlying the block stimulated.

Even in the face of such traumatic factors, however, and even though some movements formerly obtained were absent after isolation, multiplicity of representation persisted to an often startling degree (strong movements of both extremities). Furthermore, as in the experience of Dusser de Barenne and Marshall,[49] sometimes the strength of movements was intensified after segregation (experiment *B* in table 1).

facilitatory states in the brain, as suggested by Brown. It therefore appears to be more reasonable, in studying the function of the motor cortex, to record and chart its activity under conditions approaching natural stimulation than to restrict the investigation to the effect of brief threshold stimuli, which are probably never operative physiologically.

We conclude, then, that under the influence of facilitatory stimulation, which, although artificial, is of the same order as volitional control, the motor cortex does not consist of a great number of mutually exclusive and independently operative "tiles" of gray matter, the whole forming a mosaic of individual muscular repre-

49. Dusser de Barenne, J. G., and Marshall, C.: On a Release-Phenomenon in Electrical Stimulation of the "Motor" Cerebral Cortex, Science **73**:213-214, 1931.

sentation, but is, rather, a multipotential organ in which movements of different parts of the somatic musculature are broadly, although not coextensively, represented. The cortex of the brain is a tissue physiologic assay of any single part of which will reveal multipotentiality, but to a degree varying according to the part selected for examination and dependent on the species chosen.

We should reemphasize that these broad and overlapping areas of representation of movements through joints, for example, do have their limitations and that this limitation becomes the more restricted the higher one ascends in the animal hierarchy. A single instance will serve as illustration: Stimulation just below a line connecting the dimple which marks the superior precentral sulcus in the monkey brain, shown in figure 3 *C*, evoked movements of the fingers, but stimulation just above this line did not result in finger motion. Were physical or physiologic spread to account for our results, one might expect stimulation at either of these closely adjacent points to produce such a response in common, but it did not do so.

The oscilloscopic tests cited demonstrate clearly that physical spread of the stimulating current under our experimental conditions is of negligible import. However, the factor of physiologic spread cannot be entirely ignored. To be sure, multiplicity of representation of movements at a single, restricted motor "point" persisted after surgical isolation, but it was often, as tables 1, 2 and 3 demonstrate, of a lesser degree. Traumatic factors may, as noted, account for all or part of this discrepancy; so may the elimination of physiologic spread. However, even in the complete absence of the latter, multiplicity of representation is still retained.

The chief basis of our thesis rests on the isolation experiments. The tissue cut around was just large enough to accommodate the electrodes, which were close together. The incisions went deep enough into the brain to include the intergyral U fibers. In the intact brain stimulation of the cortex under conditions of primary facilitation or excitation of the cortex through volition may involve physiologic spread and, secondarily, spatial facilitation (secondary facilitation of the two forms described by Brown [31c] and Dusser de Barenne and McCulloch [39]). Since the circumsection of a small cortical area rules out physiologic spread, and thereby secondary facilitation of cortical foci not directly stimulated, it is imperative to conclude that multiple representation resides in areas at least as small as those which were isolated in our experiments. It is of interest to point out that the isolated area resembles the intact cortex not only by its retention of muliple representation but by hypothalamocortical facilitation. The effect of the latter on an isolated cortical "point" suggests that some of the loss of representation following isolation was due to trauma, which this powerful facilitatory impulse apparently partially overcame.

The anatomic basis for the extensive functional overlap described in this paper is not likely to be found in the classic cytoarchiteconic maps of the Vogts [7] and their suggested expansion by Lorento de Nó.[50] It may lie in the laminar type of anatomic research advocated by Walshe,[16] who stated in his critical review of physiologic structural correspondence in the motor cortex:

> The areas depicted on a cortical map attempt to take into account all the six component layers of the cortex, and, as it were, strike an average between them: but an ideal cortical map would require a separate sheet for each layer . . . . It seems that in the future we may have to direct our attention to a laminar physiology of the cortex rather than — as we have hitherto done—to an areal.

To this conception of the anatomic counterpart of our physiologic observations we would subscribe wholeheartedly. Multiplicity of representation under our experimental conditions undoubtedly depends on variations in cortical laminas—in particular, lamina V (the large and giant pyramidal cell layer which has been demonstrated by Dusser de Barenne and collaborators [51] to be of greatest importance in motor function). Instead of close and exclusive aggregation of all the ganglion cells in the fifth layer which have their axonal terminus on anterior horn cells going to the biceps muscle of the monkey, for example, these ganglion cells for the biceps are probably distributed, in the fifth lamina, over a very wide range of cortex. Where they are most numerous and closely arranged, stimulation may evoke a contraction of the biceps as a threshold movement or as a prime mover in a series of movements or as the movement which is of greatest magnitude in the complex. How-

50. Lorente de Nó, R.: The Cerebral Cortex: Architecture, Intracortical Connections, and Motor Projections, in Fulton,[10b] chap. 15.

51. Dusser de Barenne, J. G.: The Disturbances After Laminar Thermacoagulation of the Motor Cerebral Cortex, Brain **57**:517-526, 1934. Dusser de Barenne, J. G., and Murphy, J. P.: Thermacoagulation of Motor Cortex Exclusive of Its Sixth Layer, J. Neurophysiol. **4**::147-152, 1941.

ever, wherever there are enough of them together to produce, by combined action, any discernible contraction in the muscle innervated, facilitatory stimulation will reveal their presence. Although the cortical maps presented were drawn without reference to intensity of stimulation and magnitude of the response, differences in reaction were observed, and these differences seem best accounted for by the assumption that the specific ganglion cells responsible for a given movement are inequally distributed and of variable threshold excitability.

It should be restated here that, although we have focused our attention in this investigation on the revelation of multiplicity of representation in the motor cortex, observations leading to this conclusion have been repeatedly made since the inception of study of motor cortical physiology. Ferrier [5] early noted that "the areas [of discrete representation] have no line of demarcation from each other, and where they adjoin stimulation is apt to produce a conjoint effect peculiar to each. . . . A slight stimulus of short duration causes only a part of a complex action which is manifested in its completeness when the stimulus is of somewhat greater intensity and duration." Beevor and Horsley,[17] likewise, called attention to the lack of absolute boundaries between areas of localization and observed that "each movement had a center of maximum representation, this gradually shading off into the surrounding cortex." In recent times, Hines [18] reached similar conclusions from her experiments on the macaque, although still contending that the muscle is the final unit of representation, and Dusser de Barenne [21] emphatically denied the reality of mosaic representation in physiologic activity of the motor cortex. Finally, Clark and Ward,[42] in experiments conducted on lightly anesthetized cats, found simultaneous contractions of muscle groups in the contralateral forelimb and hindlimb, just as we did, but left the pursuance of the extent of such overlap to future investigation.

Hughlings Jackson's [14] insistence on the principle of multiple representation, lost sight of until restated by Walshe,[24] is preeminent in all of his discussions of the physiology of the motor areas in man. Horsley,[15] shortly after the turn of the last century, saw fit to make his position clear on this point:

> It should not, in my opinion, be assumed that the effect of a minimal stimulus, evoking, as it often does, but a single movement of one segment of a limb, is a criterion of all that is represented—that is, in that portion of the cortex cerebri. The response elicited from the cortex cerebri by a stimulus is within limits proportional (1) to the strength of the stimulus, and (2) to the degree to which the movements of any given segment or part of the body are represented at the point stimulated. Consequently, a minimal stimulus may only be adequate for one item of several represented at the point stimulated.

A specific and practical application of this principle may be made to a solution of the problem of the causes for return of function in a part of the body—the arm, for instance—when the primary cortical area controlling the movements of this part has been removed or irreparably damaged in toto. Jackson [14] stated the belief that such recovery took place because "the neighboring parts represent the very same region," but others since his time have attributed reparation to "reorganization" of cortical activity (Kennard [22a,b]), to ipsilateral innervation (Fulton [52]) or to activity of extrapyramidal motor areas (Foerster [20]). Although reorganization within motor areas, particularly under the influence of training (Trendelenburg [53]) and during the developmental period, is not denied, the substrate of this "reorganization" must be present. No one would argue for a transmutation of sensory ganglion cells into motor neurons or for a new formation of neurons under any conditions. It is therefore significant that the increased excitability of neurons in adjacent areas after areas 4 and 6 had been removed (Kennard) was revealed by methods of stimulation apparently similar to our own (i. e., primary facilitation). As previously demonstrated, under such stimulatory conditions these areas were found to be excitable in animals without cortical ablations, and therefore the assumption of a radical reorganization would seem to be unnecessary. The evidence cited in favor of the thesis that recovery of motor power is due to activity of the cortex ipsilateral with the lesion is unsatisfactory, since Bucy [54] showed that ipsilateral movements are represented in area 6 and are characterized by gross postural effects ("sustained extension of all joints"), in contradistinction to the specialized movements elicitable from area 4. In addition, Bucy's [23] recent study of

52. Fulton, J. F.: Bilateral Representation of the Lower Extremity in the Motor Cortex of the Chimpanzee, Am. J. Physiol. **101**:36, 1932; footnote 10 *b*.

53. Trendelenburg, W.: Untersuchungen über den Ausgleich der Bewegungsstörungen nach Rindenausschaltungen am Affengrosshirn, Ztschr. f. Biol. **65**: 103-140, 1915.

54. Bucy, P. C.: Ipsilateral Representation in the Motor and Premotor Cortex of Monkey's Brain, Brain **56**:318-342, 1933.

removal of the precentral gyrus in man leads to the conclusion that recovery of function of paralyzed extremities must be due to activity of the part of the precentral cortex remaining—and not to ipsilateral innervation (which has never been recorded for the arm, for example, in man) or to the activity of subcortical mechanism. His experiences are similar to those of Kennard,[22a] who observed greater and more enduring paralysis in contralateral single extremities in monkeys when the whole of the precentral gyrus was excised than when arm or leg areas alone were removed.

Our contention is this: If all cortex responsive in terms of leg movement under conditions of primary cortical facilitation were removed, there would be enduring paralysis of the contralateral leg, with little or no functional recovery. We agree with Jackson, Walshe and Bucy that recovery after removal of all of what is decided to be the leg area during the usual type of briefly acting, liminal, "sampling" stimulation is due to the retention of cortex controlling movements of the leg. That such complete removals would be contraindicated in the surgical treatment of choreoathetosis, when more restricted ablations suffice, is of course obvious.

There is no better way to conclude than to return to first sources and cite the words of Hughlings Jackson[14] as he summed up his beliefs concerning motor representation in the brain:

> Then it may be said that one convolution will represent only the movements of the arm, another only those of speech, another only those of leg, and so on. The facts . . . . show that this is not the plan of structure of the nervous system. Thus, to take an illustration, the external parts $x$, $y$, and $z$ are each represented by units of the corpus striatum. But the plan of representation is not that some units contain $x$ largely only, as $x_3$, others $y$ largely only, as $y_3$, but that *each* unit contains $x$, $y$, and $z$—some, let us say, as $x_3$, $y_2$, $z$, others as $x_2$, $y_3$, $z$, etc. When we come to the still higher evolution of the cerebrum, we can easily understand that, if the same plan be carried out, a square inch of convolution may be *wanting*, without palsy of the face, arm, and leg, as $x$, $y$, and $z$ are represented in other convolutions; and we can also easily understand that *discharge* of a square inch of convolution must put in excessive movement the *whole* region, for it contains processes representing $x$, $y$, and $z$, with grey matter in exact proportion to the degree of complexity.

From this we might today delete "corpus striatum" and substitute "internal capsule," but in essence this prescient quotation (1870) sums up and states our case exactly.

SUMMARY

Under conditions of suprathreshold stimulation (condenser discharges, 90 per second; stimulatory period, ten seconds) involving primary facilitation, multiplicity of representation of movements is found throughout the excitable motor cortex in three species (rabbit, cat, monkey). It is shown that the boundaries within which movements of the various joints of the arm or of the leg are elicited are practically coextensive, and a similar statement applies to the movements of the face and head. The cortical overlap is not restricted to movements represented in each of the large somatotopic areas (leg, arm, face) but transcends them. Thus, foci activating simultaneously or successively movements of the arm and leg and others calling forth contractions of muscles in the forearm and face are found. The overlap of large somatotopic areas seems to decrease with progressive encephalization, but even in the monkey the cortical map obtained under conditions of primary facilitation is far different from the accepted mosaic of representation.

Multiplicity of representation persists after isolation of a cortical focus stimulated and therefore does not depend on physiologic spread of initiated intracortical waves of impulse, nor is it due to simple physical spread of current. It is, therefore, an inherent property of the motor cortical gray matter and discretely resident within it. Movements, not muscles, are much more widely represented than the usual localization maps, obtained by threshold stimulation with briefly acting electrical currents, indicate. There are, however, boundaries within the excitable area beyond which a given movement cannot be evoked.

The anatomic substrate of the observation of multiplicity of representation in the motor cortex is thought to consist of local variations in population density of specific ganglion cells in the fifth cortical lamina. Consequently, neurons controlling certain movements are not confined to small cortical areas composing a mosaic of sharply delimited units but are interdistributed throughout relatively broad zones. Where a reaction is obtained as a prime movement, there ganglion cells distributed to the spinal segments involved are probably found in heaviest concentration and possess the lowest threshold. But the other members of a series of movements also have their local representatives, which are called into action particularly with higher intensities of stimulation. Without primary facilitation, however, excitable

foci are present only where the density of population of specific neurons is greatest and their threshold lowest. Under these conditions the well known cortical mosaic results.

Contrary to expectations, movements involving distal joints are not more widely distributed than are movements involving proximal joints. Similarly, the threshold for a given movement under conditions of primary facilitation was not necessarily lower in a cortical area where it appeared first in a sequence than in other foci where it developed as a secondary or tertiary movement.

Multiplicity of representation and extent of representation of movements far beyond the bounds delimited by threshold stimulation undoubtedly account for recovery of function of individual parts of the body after the contralateral controlling cortical area has supposedly been removed *in entirety*.

Department of Physiology, University of Minnesota.

# DISSEMINATED OLIGODENDROGLIOMA

C. M. BLUMENFELD, M.D., AND W. JAMES GARDNER, M.D.
CLEVELAND

Oligodendroglia was defined by del Río Hortega [1] in 1921. Three years later, Bailey and Hiller [2] suggested that certain gliomas were composed of oligodendrocytes. In 1926, Bailey and Cushing [3] set apart a group of brain tumors as oligodendrogliomas; this publication was soon followed by several reports of similar tumors (Dickson,[4] Schaffer [5] and Thomas and Jumentié [6]). That such tumors were composed of cells which were impregnated like normal oligodendrocytes by del Río Hortega's method was shown first by Bailey and Bucy.[7] Thus, oligodendroglioma was established as an entity. The average incidence of oligodendroglioma in the cases of glioma reported by Bailey [8]; Baker [9]; Elvidge, Penfield and Cone [10]; Gagel [11]; Környey,[12] and Löwenberg and Waggoner [13] was 3.4 per cent (74 of 2,131), ranging from 1.3 per cent of Gagel's series to 8.4 per cent of Környey's cases. From the beginning, it has been considered a glioma with a relatively good prognosis, an opinion based on frequent reports of a long antecedent history, long postoperative survival, a narrow zone of transition from tumor to uninvolved brain, few or no mitotic figures and calcification. As a result, observations which indicate that the oligodendroglioma is second only to the medulloblastoma in its propensity to become disseminated through the ventricles and the subarachnoid spaces have been neglected. The case reported here presented a diagnostic problem for fourteen years. It is an instance of disseminated oliogodendroglioma. The knowledge that this tumor may spread into the subarachnoid space might have led to an earlier diagnosis in this case and may prove helpful in the future.

From the Cleveland Clinic and the Institute of Pathology, Western Reserve University.

1. del Río Hortega, P.: Estudios sobre la neuroglia: La glia de escasas radiaciones (oligodendroglia), Arch. de neurobiol. **2**:16, 1921.

2. Bailey, P., and Hiller, G.: The Interstitial Tissues of the Central Nervous System: A Review, J. Nerv. & Ment. Dis. **59**:337-361, 1924.

3. Bailey, P., and Cushing, H.: A Classification of the Tumors of the Glioma Group on a Histogenetic Basis with a Correlated Study of Prognosis, Philadelphia, J. B. Lippincott Company, 1926.

4. Dickson, W. E. C.: Oligodendroglioma of Floor of Third Ventricle, Brain **49**:578-580, 1926.

5. Schaffer, K.: Bemerkungen zur Histopathologie des Hirngliome, Monatschr. f. Psychiat. u. Neurol. **65**:208-229, 1927.

6. Thomas, A., and Jumentié, J.: Un cas de tumeur du ventricule latéral, Rev. neurol. **2**:202-206, 1928.

7. Bailey, P., and Bucy, P. C.: Oligodendrogliomas of the Brain, J. Path. & Bact. **32**:735-751, 1929.

8. Bailey, P.: A Review of Modern Conceptions of the Structure and Classification of Tumors Derived from Medullary Epithelium, J. belge de neurol. et de psychiat. **38**:759-782, 1938.

9. Baker, A. B.: Intracranial Tumors, Minnesota Med. **23**:696-703, 1940.

10. Elvidge, A.; Penfield, W., and Cone, W.: The Gliomas of the Central Nervous System, A. Research Nerv. & Ment. Dis., Proc. (1935) **16**:107-181, 1937.

11. Gagel, O.: Ueber Hirngeschwülste, Ztschr. f. d. ges. Neurol. u. Psychiat. **161**:69-113, 1938.

12. Környey, S., cited by Löwenberg and Waggoner.[13]

13. Löwenberg, K., and Waggoner, R. W.: Gross Pathology of the Oligodendrogliomas, Arch. Neurol. & Psychiat. **42**:842-861 (Nov.) 1939.

## REPORT OF A CASE

The patient, a white man, had been struck by an automobile and sustained a fracture of the left parieto-occipital portion of the skull at the age of 10 years. Thereafter he had occasional headaches, which gradually increased in frequency to two or three a week at the age of 17; he was first seen for this complaint on Oct. 23, 1930. During the preceding month he had had "spells," lasting less than one minute, when he could not express himself. He was small, slender and well nourished. The pubic hair was scant and feminine in distribution. His voice was high pitched. There was slight contraction of the inferior temporal portion of both visual fields. A roentgenogram showed an enlarged sella and erosion of the posterior clinoid processes. Numerous additional special studies yielded no significant information. It was considered that he might have a tumor of the pituitary or hypopituitarism due to some other cause. Medical treatment was without avail. Because of persistence of headaches and increase in number of "spells," an encephalogram was made; this showed greatly dilated lateral ventricles and a slightly dilated third ventricle. At craniotomy a gray membrane resembling thickened arachnoid bulged out between the optic chiasm and the optic tracts, puncture of which released colorless fluid.

The anatomic diagnosis of a portion of the membrane was fibrosis of the pia-arachnoid.

The patient's course continued about the same for seven years with respect to the headaches and "spells"; but his general health improved, his voice deepened, he shaved more often and he was able to perform work requiring long application and mechanical skill. A roentgenogram of the skull made in December 1937,


Fig. 1.—*A*, frontal section of brain through the splenium of the corpus callosum. Note the nodular masses of tumor in the posterior horns of the lateral ventricles.

*B*, frontal section of brain through the posterior horn of the left lateral ventricle. Note focal loss of line of demarcation between the tumor in the ventricle and the white matter. There is a small nodule of tumor in the leptomeninges over the lingual gyrus.

*C*, portion of partially degenerated tumor from the left lateral ventricle, stained with mucicarmine. Note the weakly positive reaction for mucin and the basophilic concrements. × 130.

*D*, tissue removed from between the optic chiasm and the tuber cinereum at the second operation, stained with mucicarmine. Some of the fibrils and cell processes are deep red. × 130.

because of a period of more severe and numerous "spells," showed focal calcifications in the anterior ends of the inferior horns of both lateral ventricles and the posterior horn of the left lateral ventricle. On March 3, 1944 he returned because of inability to focus his eyes. During the next week there developed dizziness, tinnitus, nausea and convulsive seizures, which started in either foot and spread to the rest of the body. There were slight wasting of muscles, widespread hypotonia, absence of abdominal reflexes, sluggish knee jerks, ataxia and bilateral optic nerve atrophy. An encephalogram showed the same changes as before. A left frontal craniotomy was done on March 23. A thin-walled cyst ruptured and collapsed as the left frontal lobe was elevated, exposing a small mass of reddish gray tissue posterosuperior to the optic chiasm. A portion of this

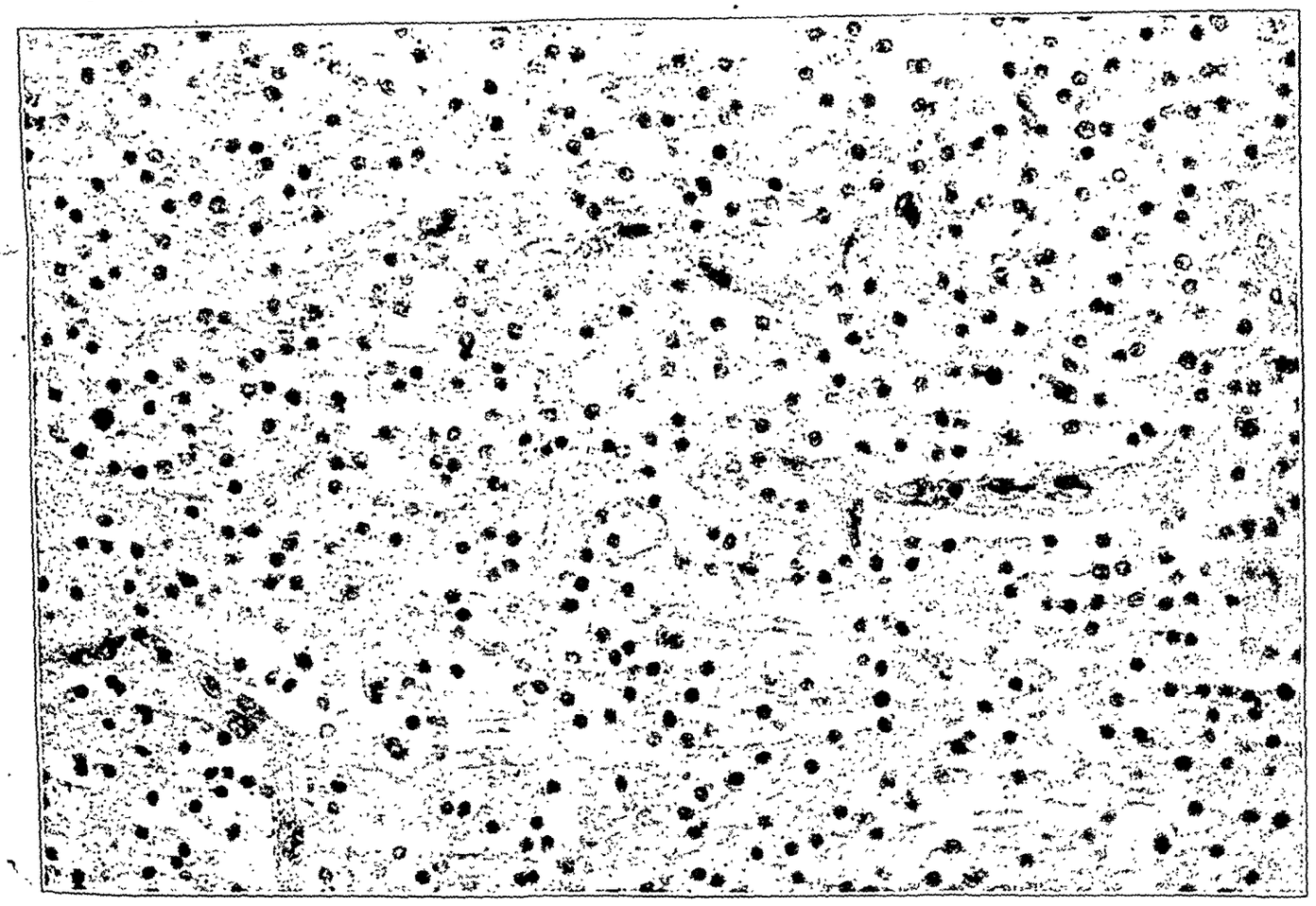


Fig. 2.—A portion of tumor from the right superior recess of the fourth ventricle. The nuclei are almost uniform in size, shape, staining reaction and distribution. The cytoplasm is not sharply delimited. Some of the cells are united by indistinct processes. Hematoxylin and eosin. × 415.

was removed. The patient died twenty-four hours after operation, thirteen years and seven months after his first admission to the hospital.

Autopsy, complete except for examination of the spinal cord, was performed sixteen hours after death by Dr. J. C. Sherrick. Observations on the brain and related structures will be given in detail. The lesions noted in the remainder of the body were as follows: slight atrophy of the thyroid gland; healed, nondeforming endocarditis of the aortic, mitral, pulmonic and tricuspid valves; slight arteriosclerosis of the aorta; slight hyperemia and edema of the lungs; primary tuberculous complex of the lower lobe of the left lung and the left inferior bronchopulmonary lymph nodes; active miliary tubercles in the liver, spleen and an accessory spleen, and slight atrophy of the testes. The thyroid gland weighed 17 Gm. and consisted of follicles of average size, filled with colloid and lined with simple low cuboidal to flat epithelium. Each testis, with the epididymis, weighed 14 Gm. A majority of the contorted seminiferous tubules showed few or no sperm heads, a reduced number of spermatids, spermatocytes and spermatogonia and an increased number of sustentacular cells. Some tubules were lined only with sustentacular cells. The interstitial cells were of average type.

The scalp, calvaria and dura showed recent and remote surgical wounds, but no trace of the remote left paricto-occipital fracture. The brain weighed 1,560 Gm. The leptomeninges were slightly thickened and reddened along the choroidal and the first part of the sylvian fissures, around the pineal and the adjacent midbrain, in the interpeduncular fossa and around the foramens of Luschka. A blood clot and friable reddish gray tissue obscured the floor of the third ventricle back to the mamillary bodies. The gyri were flattened and the sulci narrowed. The sella was enlarged; the posterior clinoid processes were eroded, and the pituitary was flattened. Section of the brain, after fixation in solution of formaldehyde U. S. P. and saline solution, revealed marked dilatation of the lateral ventricles; the third ventricle was moderately and the fourth slightly enlarged. Patches of a thin to thick layer of reddish gray, semitranslucent, soft, gelatinous material occurred on the walls of all the ventricles (fig. 1 *A* and *B*). It could be scraped from the ependymal surface with ease. The foramens of Monro were slightly narrowed, and the aqueduct of Sylvius to a greater degree by similar material, which also partially obscured but was readily separated from the choroid plexuses. In the surfaces made by section the boundary

between this material and the underlying brain was irregular in several places, notably in the region of the head of the right caudate nucleus and the right superior recess of the fourth ventricle. There was no demonstrable hypothalamus, the floor of the third ventricle being replaced by gelatinous material and blood clot.

Sections from many portions of the brain containing gelatinous material were stained with hematoxylin and eosin, Holzer's method for glia fibrils and Bodian's method for neurofibrils. Later, preparations were made with Mayer's mucicarmine stain and Penfield's combined method for oligodendroglia and microglia.

All involved portions showed abnormal tissue, interpreted as tumor, which varied in structure within a narrow range. The cells, moderately numerous to sparse, formed a reticulum in some parts, with granular, fibrillar and homogeneous eosinophilic intercellular material (fig. 2). There was slight, incomplete lobulation by slender septums, which contained small vessels formed principally of a layer of endothelium. Foci of hemorrhage were common. The tumor cells had scant, ill defined, granular, eosinophilic cytoplasm. Some had processes. The nuclei were of almost uniform size, small, round or oval, and slightly hyperchromatic, with thin membrane and regularly dispersed small chromatin granules. Some nuclei showed one or two coarser granules, but in none was an eosinophilic nucleolus noted. No mitotic figures were seen. Readily identifiable astrocytes occurred in small numbers, chiefly where the tumor involved brain tissue. Such foci were more numerous than was apparent grossly, their widespread, superficial character suggesting invasion from ventricular growth. Degeneration and necrosis were marked in portions from within the ventricles. Concrements, 25 to 500 microns in diameter, spherical or irregular, and some laminated, were numerous in ventricular portions and much less common elsewhere (fig. 3). They were more commonly basophilic and when treated by von Kossa's method gave a positive reaction for calcium. Mucicarmine preparations showed faint to deep red staining of fibrillar material but only a few patches of light pink homogeneous substance (fig. 1 *C*). Frozen sections prepared by Penfield's modification of Hortega's method for oligodendroglia (Mallory [14]) gave corroborative evidence that the tumor cells were mainly oligodendrocytes. They were impregnated about as deeply as the normal oligodendrocytes in the brain; the nuclei were similar in appearance, and an occasional cell had a few short processes (fig. 4). Astrocytes were faintly impregnated, larger, more richly branched and fibrillated. Holzer preparations showed glia fibers in the regions containing astrocytes.

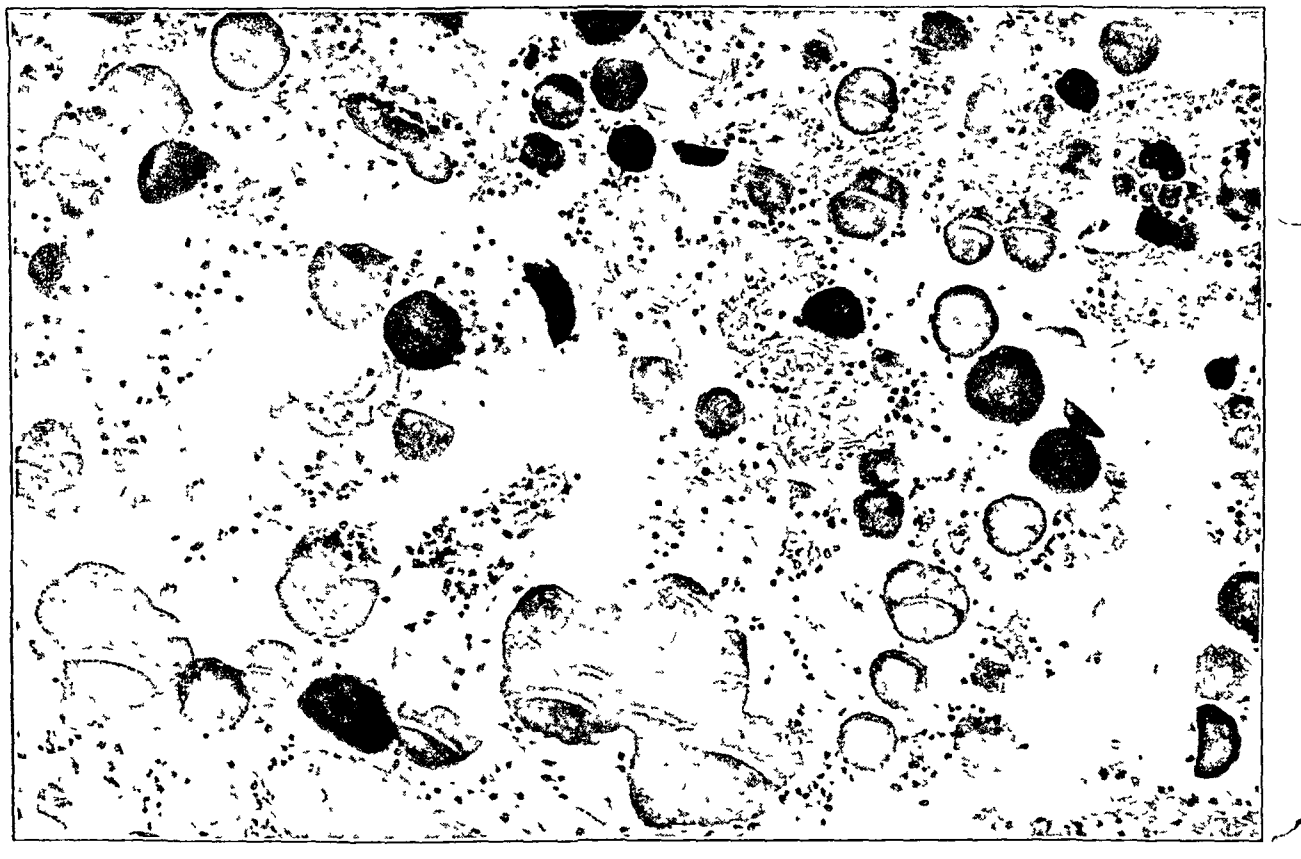


Fig. 3.—A portion of tumor from within the posterior horn of the right lateral ventricle. In addition to the numerous concrements, note the greater dispersion of the tumor cells. Material in some of these spaces stained feebly with mucicarmine. Some of the cell processes were deeply stained. Hematoxylin and eosin. × 210.

In the first surgical specimen, removed in 1930, there were small groups of cells with uniform, round, finely granular nuclei in collagenous fibrous tissue. The rest of the material was stained with mucicarmine but lacked the cells with round nuclei. The second surgical specimen was identical in appearance with the tumor seen at autopsy (fig. 1 *D*).

14. Mallory, F. B.: Pathological Technique, Philadelphia, W. B. Saunders Company, 1938, p. 254.

COMMENT

The tumor in this case is considered to be an oligodendroglioma. The nuclei were like those of oligodendrocytes.[15] The cytoplasm contained no fibrils. In Hortega preparations the tumor cells were impregnated about as deeply as the normal oligodendrocytes, and some showed a few short processes. There was a questionably positive reaction for mucin. The tumor occurred on the walls of all the ventricles, involved the brain substance superficially in many places and was identified in the leptomeninges around the hypothalamus, the beginning of the sylvian fissures and just outside the foramens of Luschka.

Fig. 4.—Intraventricular portion of tumor, prepared according to Penfield's modification of del Río Hortega's method for oligodendroglia. At about the center is a cell with two thick processes which leave the plane of focus. The nuclei of these cells are identical in appearance with those of well impregnated oligodendrocytes in the brain. × 1,245.

In textbooks and monographs dealing with the clinical or pathologic aspects of gliomas, such as those by Biggart[16]; Bailey[17]; Bailey and Cushing[3]; Bucy[18]; Cushing[19]; Elvidge, Penfield and Cone,[10] and Weil,[20] no mention is made of dissemination of oligodendroglioma. Hassin[21] referred briefly to a case of Kwan and Alpers[22] in which tumor occurred in the leptomeninges of the sylvian fissure after removal of a tumor in the frontal region.

Observations on the spread of gliomas are not numerous, probably in part the result of syllogistic reasoning. The presence of spinal metastases in a case of cerebral glioma led Cairns and Russell[23] to include removal of the spinal cord in the next 22 autopsies in cases of cerebral glioma. They found spinal subarachnoid metastases in 8 cases, in 3 of which the tumor was a medulloblastoma, in 1 an astrocytoma, in 1 an ependymal glioma, in 1 a glioblastoma multiforme, in 1 a neuroepithelioma of the retina and in 1 an unclassified glioma. Nelson[24] described an instance of histologically verified metastases of medulloblastoma to the centrums of thoracic vertebrae, emphasizing the accidental nature of the observation. Van Wagenen[25] noted widespread ependymal implantation of papilloma of the choroid plexus, a condition present in 5 of 45 cases he collected from reports by others. That medulloblastoma frequently is disseminated through the subarachnoid space is well known. That such spread is not rare with other gliomas is less well known.

Brief comments indicating that oligodendroglioma may be less benign than is usually thought were made by Cushing,[19] Eisenhardt[26] and Elvidge, Penfield and Cone.[10] This is surprising, in view of a series of reports which began shortly after Bailey and Cushing[3] first presented the entity of oligodendroglioma. Dickson,[4] in 1926,

15. Dr. Percival Bailey examined the hematoxylin and eosin preparations and stated that the tumor cells, because of the structure of the nuclei, were probably oligodendrocytes.

16. Biggart, J. H.: Pathology of the Nervous System, Baltimore, William Wood & Company, 1936, pp. 263-265.

17. Bailey, P.: Cellular Types in Primary Tumors of the Brain, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, sect. 18, pp. 941-942.

18. Bucy, P. C.: Tumors of the Brain, in Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1921, vol. 9, p. 663.

19. Cushing, H.: Intracranial Tumours, Springfield, Ill., Charles C Thomas, Publisher, 1932.

20. Weil, A.: A Text-Book of Neuropathology, Philadelphia, Lea & Febiger, 1933.

21. Hassin, G. B.: Histopathology of the Peripheral and Central Nervous System, ed. 2, New York, Paul B. Hoeber, Inc., 1940, pp. 484-487.

22. Kwan, S. T., and Alpers, B. J.: The Oligodendrogliomas, Arch. Neurol. & Psychiat. **26**:279-321 (Aug.) 1931.

23. Cairns, H., and Russell, D. S.: Intracranial and Spinal Metastases in Gliomas of the Brain, Brain **54**: 377-420, 1931.

24. Nelson, A. A.: Metastases of Intracranial Tumors, Am. J. Cancer **28**:1-12, 1936.

25. Van Wagenen, W. P.: Papillomas of the Choroid Plexus, Arch. Surg. **20**:199-231 (Feb.) 1930.

26. Eisenhardt, L.: Long Postoperative Survivals in Cases of Intracranial Tumor, A. Research Nerv. & Ment. Dis., Proc. (1935) **16**:390-416, 1937.

described an oligodendroglioma of the floor of the third ventricle which involved the leptomeninges of the interpeduncular fossa. Cairns,[27] in 1929, reported the presence of tumor deposits in the posterior horns of the lateral ventricles, the left foramen of Monro and the fourth ventricle approximately three and a half years after operative removal of an oligodendroglioma from the right frontal lobe. In 1931, Martin[28] reported diffuse ventricular spread about one year after removal of a left parietal oligodendroglioma. There was a nodule of tumor in the scalp just anterior to a cerebral hernia at the site of operation. Also in 1931, Kwan and Alpers[22] presented 4 cases of oligodendroglioma, in 1 of which a nodule of tumor was noted in the leptomeninges of the left sylvian fissure at autopsy fourteen months after removal of a left frontal tumor. Kernohan,[29] in 1932, noted recurrence and subarachnoid spread in only 1 of 52 cases of tumor of the spinal cord, that of an oligodendroglioma. A similar tumor of the filum terminale, only partially removed, recurred not only with subarachnoid spread but with invasion of skeletal muscle bordering on the wound.

Greenfield and Robertson,[30] in 1933, described 5 cases of oligodendroglioma. In 2 there were ventricular deposits and in 1 subarachnoid, as well as ventricular, spread. Löwenberg and Waggoner,[13] in 1939, from a study of 21 cases, stated, "the oligodendrogliomas have a definite tendency to invade the leptomeninges, and in some cases also the pachymeninges"; and, from a study of the literature, "oligodendrogliomas in general tend to invade the ventricular system." Finally, Beck and Russell,[31] in 1942, presented 4 cases in which occurred diffuse spread of oligodendroglioma through the subarachnoid space, with ependymal deposits in 3 of them, for which they coined the term "oligodendrogliomatosis of the cerebrospinal pathway." They stressed the presence of mucinous degeneration of the tumor as a feature of diagnostic importance. The basis for the presence of mucin lies in the tendency of oligodendroglia undergoing degeneration to form mucin, as shown by Grynfeltt,[32] by Bailey

*Data in Twelve Cases of Disseminated Oligodendroglioma*

| Author | Age at Death, Years | Sex | Duration, Years | Site of Tumor | Hydrocephalus | Mucin | Calcification Roentgenogram | Calcification Section |
|---|---|---|---|---|---|---|---|---|
| Dickson[4] | 6 | M | ½ | Hypothalamus; basal cistern; interpeduncular fossa | All | Stain not done | — | — |
| Martin[28] | 44 | M | 4 | Left parietal and occipital lobes; all ventricles; scalp (operative site) | Not mentioned | Stain not done | + | + |
| Greenfield and Robertson[30] | 16 | F | 1 | Third ventricle and iter | 1, 2 and 3 | + | — | — |
| | 44 | M | ¾ | Right frontal lobe; right lateral, third and fourth ventricles | Not mentioned | + | — | — |
| | 50 | F | 7 | Iter; fourth ventricle; pontile and basilar cisterns | All | + | — | — |
| Löwenberg and Waggoner[13] | 17 | M | ? | Septum pellucidum; lateral and third ventricles | 1 and 2 | Stain not done | — | — |
| | 51 | F | 14 | Septum pellucidum, fornices, corpus callosum, tuber cinereum, all ventricles, diffuse in leptomeninges, parts of cortex | Not mentioned | Stain not done | — | — |
| Beck and Russell[31] | 36 | M | 7 | All ventricles; diffuse in leptomeninges | All | + | — | — |
| | 42 | M | 1½ | Tuber cinereum; all ventricles; diffuse in leptomeninges | All | + | — | — |
| | 6 | F | ½ | Right frontal lobe; lateral and fourth ventricles; diffuse in leptomeninges; dura of right frontal region | All | + | + | Not mentioned |
| | 4 | F | ½ | Diffuse in leptomeninges; cerebellar cortex, optic chiasm | All | + | — | — |
| Blumenfeld and Gardner | 31 | M | 14 | Hypothalamus; all ventricles; focal in leptomeninges | All | ± | + | + |

27. Cairns, H.: A Study of Intracranial Surgery, Medical Research Council, Special Report Series no. 125, London, His Majesty's Stationery Office, 1929.

28. Martin, J. P.: Two Cases of Oligodendroglioma with Remarks on the General Clinical Features of Such Cases, Brain **54**:330-349, 1931.

29. Kernohan, J. A.: Primary Tumors of the Spinal Cord and Intradural Filum Terminale, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, sect. 20, pp. 1014-1015.

30. Greenfield, J. G., and Robertson, E. G.: Cystic Oligodendrogliomas of the Cerebral Hemispheres and Ventricular Oligodendrogliomas, Brain **56**:247-264, 1933.

31. Beck, D. J. K., and Russell, D. S.: Oligodendrogliomatosis of the Cerebrospinal Pathway, Brain **65**:352-372, 1942.

32. Grynfeltt, E.: Mucocytes et leur signification dans les processes d'inflammation chronique des centres cérébrospinaux, Compt. rend. Soc. de biol. **89**: 1264-1266, 1923.

33. Bailey, P., and Schaltenbrand, G.: Die muköse Degeneration der Oligodendroglia, Deutsche Ztschr. f. Nervenh. **97**:231-237, 1927.

and Schaltenbrand,[33] by Grinker and Stevens [34] and by others.

Eleven cases have been collected from reports by other authors in which the tumor showed ventricular or meningeal dissemination or both, exclusive of cases in which dissemination was limited to the region traversed by operation. Pertinent data are given in the accompanying table. The duration of clinically recognized disease varied from one-half to fourteen years. Of the 12 cases, headache occurred in 11; various visual disturbances were present in 9; nausea, vomiting or both was experienced in 9, and disturbances of mentality or personality were exhibited in 8. Hydrocephalus was present in 9 cases. Tumor involved the ependyma in 11 cases and the leptomeninges in 8 cases. Stains for mucin were made in 8 cases, with a questionable or weakly to strongly positive reaction in all. In none did the stain for mucin give definitely negative results. Calcification appeared in 4 cases—in both roentgenograms and sections in 2, in roentgenograms only in 1 and in sections only in 1.

There are no distinctive symptoms or signs. Two observations may prove helpful in making a diagnosis. If, at operation, there is focal or diffuse thickening of the leptomeninges, a stain for mucin should be made on a biopsy specimen, and a portion should be properly fixed for the del Río Hortega method. Foci of calcification within the ventricles should suggest this tumor.

The frequent presence of this tumor on and in ependyma lends support to the cell lineage schemes of Kernohan and Fletcher-Kernohan [35] and of Globus and Kuhlenbeck.[36] The former derived oligodendroglia from primitive ependymoepithelium, because of the presence in cellular ependymomas of cells morphologically indistinguishable from oligodendrocytes. The latter suggested that oligodendroglia may be derived from spongioblasts or bipotential mother cells of the subependymal cell plate.

34. Grinker, R. R., and Stevens, E.: Mucoid Degeneration of the Oligodendroglia and the Formation of Free Mucin in the Brain, Arch. Path. **8**:171-179 (Aug.) 1929.

35. Kernohan, J. A., and Fletcher-Kernohan, E. M.: Ependymomas: A Study of 109 Cases, A. Research Nerv. & Ment. Dis., Proc. (1935) **16**:182-209, 1937.

36. Globus, J. H., and Kuhlenbeck, H.: The Subependymal Cell Plate (Matrix) and Its Relationship to Brain Tumors of the Ependymal Type, J. Neuropath. & Exper. Neurol. **3**:1-35, 1944.

## SUMMARY

The man whose case is reported herein, 31 years old at the time of his death, had an oligodendroglioma in the cerebral ventricles for at least fourteen years. The tumor apparently originated in and subsequently destroyed the hypothalamic region. Early in its course it involved the basilar leptomeninges.

Data from the case and from 11 other cases reported in the literature showed that the time elapsing between onset of symptoms and death varied from one-half to fourteen years. Localizing symptoms and signs were absent in most cases. In three fourths or more of the cases headaches, visual disturbances, mental abnormalities, personality changes, nausea, vomiting or hydrocephalus occurred. The ependyma was involved in 11 cases and the leptomeninges in 8. Mucin was questionably or definitely present in the tumor in all cases in which a special stain was made. The morphologic features of the tumor in the leptomeninges may be obscured by fibrosis, in which instance a stain for mucin may be of value. Focal calcification of the tumor occurred in 4 cases and was demonstrated roentgenographically in 3 of these. Focal calcification seen in the ventricles roentgenographically should suggest ventricular oligodendroglioma.

Data from this case, and from other reported cases, furnish a basis for the opinion that oligodendroglioma may be neither as localized nor as slow growing as is usually thought. In its tendency to become disseminated through the cerebrospinal pathway oligodendroglioma is exceeded only by medulloblastoma.

808 Medical-Dental Building, Sacramento 14, Calif.

Ninety-Third Street and Euclid Avenue.

# BLOOD SUPPLY OF PERIPHERAL NERVES

## PRACTICAL CONSIDERATIONS

SYDNEY SUNDERLAND
MELBOURNE, AUSTRALIA

The blood supply of the larger peripheral nerves in man has been described in considerable detail in two prevous publications (Sunderland [1]). The purpose of the present communication is to outline briefly certain refinements of operative technic which are suggested by the anatomic study of the arrangement and distribution of the arteriae nervorum and which may prove of value in effecting improvements in surgical procedures carried out on peripheral nerves. The reader is referred to the previous two papers for details concerning the general and topographic features of the blood supply of the individual peripheral nerves.

It has been demonstrated that in certain regions along its course a nerve is often securely and intimately attached to an adjacent arterial channel by short nutrient arteries. Examples are provided by the ulnar nerve in the condylar groove and in the distal two thirds of the forearm; by the sciatic nerve, which is frequently securely attached to the perforating anastomotic arterial chain in the thigh, and by the anterior and posterior tibial nerves in the leg. The free and extensive mobilization of nerves is frequently required in peripheral nerve surgery, either to permit the transposition of the nerve to a new bed or, when it is being separated from surrounding attachments, to facilitate approximation of the ends after the loss of a segment. Such procedures obviously necessitate the division of any arteriae nervorum which bind the nerve to an accompanying major arterial channel, and on occasion this does involve the sacrifice of many large nutrient vessels. The question which naturally arises is whether or not such a loss will jeopardize, seriously or otherwise, the nutrition of the nerve.

Fortunately, each peripheral nerve is abundantly vascularized throughout its entire length by a succession of vessels which, by their repeated division and anastomosis on and within the nerve, outline an unbroken intraneural vascular net. A distinctive feature of this pattern is the considerable overlap of supply which obtains between the nutrient arteries entering at different levels. It is also common to see one or several longitudinally arranged macroscopic vessels, arteriolar in type, on the surface of large peripheral nerves. These superficial longitudinal channels, which are of variable, but often extensive, length, are reenforced at intervals by new arteriae nervorum. The profuse anastomosis insured by this arrangement renders it unlikely that any nutrient artery will dominate the intraneural circulation in any particular segment of a nerve.

During this investigation nerves have frequently been stripped at operation of all surrounding connections for distances of up to 15 cm., and yet when the nerve was divided distally the cut end of the freed section continued to bleed. Preparatory to its transposition anterior to the humeral epicondyle, the ulnar nerve has been mobilized over corresponding distances without in any way retarding or impairing the improvement in conduction which usually follows such a procedure. The experimental work of Adams,[2] who has recently investigated the effects of exclusion of the regional sources of supply on the sciatic nerve of the rabbit, and the investigations of Bentley and Schlapp [3] on the blood supply of nerves in the cat support this belief in the efficiency of the collateral circulation in the nerve. The problem, however, assumes importance when all the vessels to a 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.

From the Department of Anatomy and Histology, University of Melbourne.

1. Sunderland, S.: The Blood Supply of the Nerves of the Upper Limb in Man, Arch. Neurol. & Psychiat. **53**:91 (Feb.) 1945; The Blood Supply of the Sciatic Nerve and Its Popliteal Divisions in Man, ibid., this issue, p. 283.

2. 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.

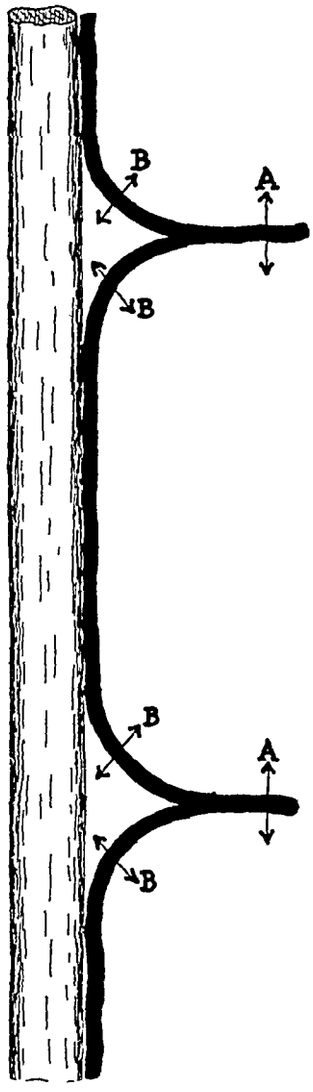
3. Bentley, F. H., and Schlapp, W.: Experiments on the Blood Supply of Nerves, J. Physiol. **102**:62, 1943.

Admittedly, there are occasions, though they are infrequent, when one nutrient artery would appear to supply long stretches of a nerve without reenforcement, but it has been found, from an examination of sectioned and injected material, that even under these apparently adverse conditions of supply the anastomosis is of such dimensions at the peripheral limits of the solitary channel that there is only a remote possibility that segmental ischemia would result from the blocking of such a single nutrient vessel.

The manner in which the arteriae nervorum are divided when one is freeing the nerve is of some significance. In the event of the obstruction of one or more entering nutrient vessels, the circulation is maintained by vessels coursing in the crevices between the fasciculi and the large longitudinal anastomosing channels on the surface of the nerve. Should the superficial system be interrupted, vascularization of the nerve then depends solely on the collateral circulation established by the intraneural pattern within the nerve, and the vessels composing the latter are not always as large as those on the surface. Consequently, when one is stripping the nerve from its surroundings, it is advisable to preserve, wherever possible, the superficial longitudinal pathway. Reference to the accompanying diagram (figure) will make this point clear. The superficial pathway will be preserved if the nutrient vessels are divided as far from the nerve as is possible and convenient (at point *A*) and before they have branched into their ascending and descending limbs. If the nerve is roughly and carelessly dissected or stripped from its bed, these delicate channels are likely to be torn at the site where they enter the nerve (at points *B*), interrupting thereby the superficial system on the surface of the nerve, a disturbance which, in turn, is liable to embarrass the intraneural circulation. Where there is more than one superficial longitudinal channel, which is often the case, the destruction of one can be adequately compensated for, but the presence of such multiple superficial channels cannot be relied on.

The appropriate disposal of the arteriae nervorum when one is freeing a nerve from adjacent tissues is often greatly aided by a knowledge of the regional sources of supply to the nerve and the point at which the latter is usually securely anchored to adjacent arteries by short, stout arteriae nervorum. Furthermore, should a large nutrient vessel be torn or inadvertently divided at the surface of the nerve, it may retract into the epineurium and cause troublesome hemorrhage, while attempts to secure the vessel may cause damage to superficial fasciculi. Such a complication can be avoided by planned ligation of the vessels at some distance from the nerve.

It is customary to execute operations on peripheral nerves under tourniquet control. Under such conditions nutrient arteries may be severed and retracted unnoticed within the nerve. These may bleed postoperatively into the intraneural tissues and subsequently result in scarring, which, in turn, may imperil nerve fibers. Since large vessels on and within the nerve are occasionally severed when freshening nerve ends preparatory to suture, it is advisable to release




Superficial blood supply of the peripheral nerve.

the tourniquet during this procedure in order to determine whether any substantial "bleeders" are presenting at the nerve ends. If hemorrhage reaches proportions which demand mechanical control, it is important to remember that any but the most delicate attempts to secure the severed vessels will inevitably result in damage to the fasciculi. It is conceivable that failure to control extensive bleeding at and about the suture line may ultimately lead to scarring and thereby introduce an additional factor in retarding and limiting regeneration. Capillary bleeding is usually controlled by the suture, but even

here postoperative oozing may lead to similar complications.

Intraneural hemorrhage can reach considerable proportions in the sciatic nerve (where the main intraneural channels are often of large caliber), and this may be one of the factors leading to irreparable changes in the nerve following trauma which does not result in any break in continuity of the nerve. There is also some evidence (personal observations) to suggest that occasionally fusiform swellings on the nerve at the site of injury are partly the result of the organization of hematomas which have split and separated the fasciculi.

The manner in which the large arteries and nerves of a limb may be closely and tightly knit into a common neurovascular bundle should also be borne in mind when ligating arteries—it is not unknown for the inexperienced to ligate the nerve with the artery.

The anastomoses, on and within the nerve, between nutrient arteries derived from different and widely separated major arteries form the basis for the development of collateral circulations when the major arterial channel to a limb has been interrupted. Collateral circulations of this type and their importance in maintaining the circulation of the limb have been reported on by various investigators (Porta,[4] Holl,[5] Hyrtl,[6] Zuckerkandl,[7] Quénu and Lejars,[8] Tonkoff,[9] Makins [10]).

4. Porta, L.: Delle alterazioni patologiche delle arterie per la legatura e la torsione, esperienze ed osservazioni, Milan, G. Bernardoni di Gio, 1845; cited by Tonkoff.[9]

5. Holl, M.: Zerreissung der Kniekehlen—Gefasse und Nerven bei Streckung einer Kontraktur, Arch. f. klin. Chir. **22**:374, 1878; Verrenkung des linken Ellbogengelenkes mit Zerreissung der A. ulnaris und der N. medianus und ulnaris; Heilung; Collateral-Kreislauf, Med. Jahrb., 1880, p. 151.

6. Hyrtl, J.: Lehrbuch der Anatomie des Menschen, Vienna, W. Braumüller, 1881.

7. Zuckerkandl, O.: Zwei Fälle von Collateralkreislauf, Med. Jahrb. **15**:273, 1885; cited by Poirier, P., and Charpy, A.: Traité d'anatomie humaine, ed. 2, Paris, L. Battaille & Cie, 1901, vol. 3, p. 633.

8. Quénu, J., and Lejars, F.: Etude anatomique sur les vaisseaux sanguins des nerfs, Arch. de neurol. **23**:1, 1892.

9. Tonkoff, W.: Die Arterien der Intervertebralganglien und der Cerebrospinalnerven des Menschen, Internat. Monatschr. f. Anat. u. Physiol. **15**:353; 1898.

10. Makins, G. H.: Gunshot Injuries to Blood Vessels, Bristol, J. Wright & Sons, 1919.

# BLOOD SUPPLY OF THE SCIATIC NERVE AND ITS POPLITEAL DIVISIONS IN MAN

SYDNEY SUNDERLAND

MELBOURNE, AUSTRALIA

The results of an anatomic study of the blood supply of the peripheral nerves of the upper limb in man have been described in a previous paper (Sunderland [1]). The investigation which forms the subject of the present report represents an extension of those studies and covers the blood supply of the sciatic nerve and its popliteal divisions.

## REVIEW OF LITERATURE

Information concerning the blood supply of the sciatic nerve and its divisions is contained in the works of Haller,[2] Walter,[3] Hyrtl,[4] Henle,[5] Holl,[6] Quénu and Lejars,[7] Bartholdy,[8] Tonkoff,[9] Chaumet, Heymann and Mouchet,[10] Portal,[11] Rauber [12] and Sappey.[12] Their descriptions are, however, with the exception of those by Tonkoff and Bartholdy, brief and incomplete and cover only sections of the nerve. The present investigation was undertaken to extend the observations of Tonkoff and Bartholdy and was based on a much larger series of adult specimens than has hitherto been examined. Their results can be most appropriately reviewed in the sections of the text devoted to a description of the regional sources of supply to the nerve.

## MATERIAL

Observations were made on the nutrient arteries to the sciatic nerve and its popliteal divisions in 40 adult dissected specimens. In each specimen the nerves were examined from the point where the sciatic nerve emerged from the pelvis to the level of the malleoli. The arrangement of the intraneural vascular pattern was studied microscopically in histologic sections prepared from segments of the nerves taken at the following levels: gluteal region; upper, middle and distal thirds of the thigh; popliteal fossa; neck of the fibula, and upper, middle and distal thirds of the lower portion of the leg.

## EXTRANEURAL AND INTRANEURAL VASCULAR PATTERN

Reference should be made to the original paper (Sunderland [1]) for a detailed account of the general features relating to the extraneural and intraneural disposition of the vasa nervorum, since these have a general application which covers the sciatic nerve. The following additional features are worthy of note in connection with the angioarchitecture of this nerve and its divisions:

1. The largest arteriae nervorum observed in the upper and lower limbs were those supplying the sciatic nerve in the buttock and thigh. They were arteriolar in type and were provided by the inferior gluteal artery and the perforating anastomotic chain.

2. As in the upper limb, nutrient arteries of the direct type predominated; the number of the indirect type in the leg exceeded that in the thigh and buttock.

From the Department of Anatomy and Histology, University of Melbourne.

1. Sunderland, S.: The Blood Supply of the Nerves of the Upper Limb in Man, Arch. Neurol. & Psychiat. **53**:91 (Feb.) 1945.

2. Haller, A.: Icones anatomicae quibus præcipue aliquæ partes corporis humani delineatæ proponuntur et arteriarum potissimum historia continetur, Göttingen, A. Vanderhoeck, 1756.

3. Walter, F. A.: Angiologisches Handbuch, zum Gebrauch seiner Zuhörer, Berlin, G. A. Lange, 1789; cited by Bartholdy.[8]

4. Hyrtl, J.: Ueber normale und abnorme Verhältnisse der Schlagadern des Unterschenkels, Vienna, K. Gerold's Sohn, 1864.

5. Henle, J.: Handbuch der systematischen Anatomie des Menschen, Braunschweig, F. Vieweg u. Sohn, 1868, vol. 3, pt. 1.

6. Holl, M.: Zerreissung der Kniekehlen-Gefässe und Nerven bei Streckung einer Kontraktur, Arch. f. klin. Chir. **22**:374, 1878.

7. Quénu, J., and Lejars, F.: Étude anatomique sur les vaisseaux sanguins des nerfs, Arch. de neurol. **23**:1, 1892.

8. Bartholdy, K.: Die Arterien der Nerven, Morphol. Arb. **7**:393, 1897.

9. Tonkoff, W.: Die Arterien der Intervertebralganglien und der Cerebrospinalnerven des Menschen, Internat. Monatschr. f. Anat. u. Physiol. **15**:353, 1898.

10. Chaumet, G.; Heymann, and Mouchet: Note sur la topographie des artères des nerfs sciatiques, Bull. et mém. Soc. anat. de Paris **18**:404, 1921.

11. Portal, A.: Cours d'anatomie médicale, Paris, Baudouin, 1804, vol. 3; cited by Bartholdy.[8]

12. Cited by Tonkoff.[9]

3. The T-shaped division was the most common pattern assumed by a nutrient artery when it reached the nerve. In the case of the arteries provided by the crucial anastomosis and the branches from the perforating arteries, the ascending limb of the T was often larger than the descending limb. This was uncommon in the arm.

4. Though large nutrient vessels were occasionally observed descending for long distances on the surface of the sciatic trunk, such vessels usually entered the nerve either immediately on reaching it or after a short course on its surface. They then passed to the interval between the two divisions and as they descended branched into the interfascicular spaces (fig. 1 *A*).

In an investigation of the paralysis induced by direct pressure and by tourniquet in the sciatic nerve of the cat, Denny-Brown and Brenner [13] observed that the lesions produced in their experiments were maximal in the peroneal division just below the bifurcation of the sciatic nerve. They compared this observation with the reported differences in vulnerability of the medial and the lateral popliteal nerve in man to apparently similar injurious agents and explained the relative susceptibility of the two branches as follows:

> Besides the obvious difference in size of the two nerves, the peroneal division is usually in the form of one major bundle, so that its vessels have less protection than those of the popliteal division, which lie in the crevices between the bundles. This anatomic difference may certainly account for the difference in lesions caused by pressure.

They did not, however, make it clear whether their explanation applied to man, to the cat or to both.

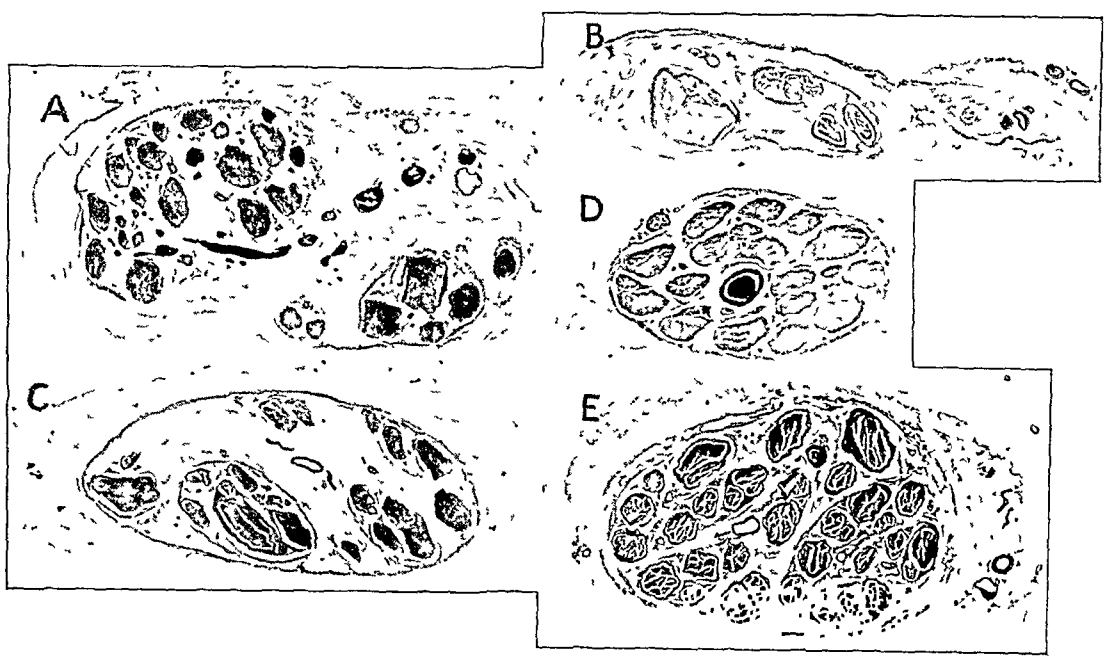



Fig. 1.—*A*, photomicrograph (× 6) of a transverse sciatic nerve in the thigh, illustrating the presence of multiple major arterial channels between its two divisions and the mode of branching into the fasciculi; *B*, photomicrograph (× 4.5) of a transverse section of the lateral popliteal nerve at the neck of the fibula, demonstrating (a) the thinning and flattening of the trunk, (b) the presence of many fasciculi and (c) the exposed position of the nutrient vessels (88 per cent of specimens); *C*, photomicrograph (× 8) of a transverse section of the lateral popliteal nerve at the neck of the fibula, demonstrating the central position occupied by the major nutrient channels (12 per cent of specimens); *D*, photomicrograph (× 8) of a transverse section of the posterior tibial nerve, showing a centrally situated major arterial channel (this is the common arrangement), and *E*, photomicrograph (× 8) of a transverse section of the posterior tibial nerve, showing a peripherally situated major arterial channel (this is an unusual arrangement).

5. In the popliteal fossa the largest arterial channels coursed on or within the nerve. As the lateral popliteal (common peroneal) nerve approached the neck of the fibula, the major intraneural vessels were observed to occupy a superficial and exposed position in 88 per cent of the specimens and a deep and protected position between the fasciculi in only 12 per cent (fig. 1 *B* and *C*). The disposition of the nutrient vessels and fasciculi in this region is of special significance.

In no specimen in the present investigation was the lateral popliteal nerve composed of a single bundle. Furthermore, there was no fea-

13. Denny-Brown, D., and Brenner, C.: Paralysis of Nerve Induced by Direct Pressure and by Tourniquet, Arch. Neurol & Psychiat. **51**:1 (Jan.) 1944.

ture of the intraneural vascular pattern which was specific to this nerve or which would adequately account for the susceptibility of this nerve to pressure. In a recent investigation devoted to a study of the adipose tissue content of peripheral nerves (to be reported elsewhere), it has been demonstrated that the lateral division of the sciatic nerve and the lateral popliteal nerve usually contain less supporting adipose tissue than the medial division and the medial popliteal nerve, and I am convinced that this morphologic difference provides a more satisfactory explanation for the susceptibility of this nerve to pressure.

At the neck of the fibula the lateral popliteal nerve was usually flattened and thined against a firm, resistant surface, was composed of many small fasciculi, was commencing to separate into its divisions and, as a rule, contained very little supporting adipose tissue. In addition, the associated nutrient vessels usually occupied an exposed or relatively exposed position (fig. 1 *B*). I believe that it is a combination of these morphologic features which predisposes the nerve to compression injuries at this site.

6. As a rule the intraneural plexus in the buttock and thigh contained several arterial channels of fairly large caliber whereas below the knee one major vessel usually dominated the plexus and generally, but not invariably, occupied a central position (fig. 1 *A, D* and *E*).

7. The manner in which the intraneural vascular pattern was established was fundamentally the same in the sciatic trunk and its medial and lateral popliteal branches, and the terminal capillary meshwork was, 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 were subject to such a considerable range of variation in different subjects, as well as at different levels in the same nerve, that no two patterns were alike in detail. There was certainly no pattern which was constant or characteristic for any section of the nerve. Moreover, the form taken by the pattern was quite unpredictable. The differences appeared to be due to minor variations in the pattern designed to provide the most effective blood supply to the nerve in terms of its anatomic structure. There was a suggestion that they were, 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; these are known to be variable morphologic features.

Though a comparison of the intraneural vascular pattern of two segments of the nerve will reveal obvious differences, the evidence suggests that there is nothing in those differences to indicate that one receives a better or a poorer blood supply than the other.

## REGIONAL SOURCES OF SUPPLY

The source and number of the nutrient arteries are set out in tables 1 and 2. In 11 specimens the sciatic nerve divided high in the thigh or emerged from the pelvis in two divisions. The data on these specimens have been presented separately.

For the sake of convenience, no distinction has been drawn in the tables between nutrient arteries of the direct and those of the indirect type. Nutrient arteries included under the heading of muscular were traced into the nerve from fine muscular branches, the parent stem of which could not be ascertained with certainty.

### GLUTEAL REGION

Nutrient arteries were traced intraneurally into the sciatic nerve from the sacral plexus. The origin of these vessels was not established.

*Inferior Gluteal Artery.*—The major supply to the nerve in the buttock was provided by the inferior gluteal artery (one to six branches), which supplied the nerve in all but 4 specimens.

On entering the buttock the inferior gluteal artery descended medial to the nerve. The nutrient arteries approached the nerve from the medial side and, after a course of variable length on the surface of the nerve, entered its inner margin, deep or superficial surface. Occasionally large branches of the gluteal artery crossed superficially or deep to the nerve in this situation and supplied it as they did so. It was unusual for a nutrient artery to approach and enter the nerve from the lateral aspect—when this occurred the twig was small and was derived from a muscular branch.

Hyrtl,[4] Henle,[5] Holl,[6] Quénu and Lejars[7] and Rauber[12] described a nutrient vessel from the inferior gluteal artery, and this is now universally recognized as the arteria comitans nervi ischiadici. Bartholdy[8] objected to this term on the grounds that this branch is a true nutrient artery and, moreover, is not the only nutrient twig supplied by the gluteal artery. He claimed that the inferior gluteal artery gave a branch to the nerve in the pelvis and two in the buttock, with an additional supply from the branches to

TABLE 1.—*Source and Number of Nutrient Arteries to the Sciatic Nerve in Man* *

| Specimen No. | Buttock | | Thigh | | Popliteal Fossa | | | | | | | | | Leg | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Medial Popliteal | | | | Lateral Popliteal | | | | | Posterior Tibial | | | Anterior Tibial | Musculocutaneous |
| | Inf. Glut. | Cruc. | Perf. | Pop. | Perf. | Pop. | Gen. | Musc. | Perf. | Pop. | Gen. | Musc. | C. Fib. | Post. Tib. | Peron. | Musc. | Ant. Tib. | Ant. Tib.-Peroneal |
| 1 R | 2 | 1 | 3 | .. | .. | .. | 1 | 1 | .. | .. | .. | .. | .. | 9 | 1 | .. | 9 | 3 |
| 1 L | 1 | 1 | 3 | 1 | .. | .. | .. | 2 | .. | .. | .. | 2 | 1 | 8 | .. | 1 | 12 | 3 |
| 2 R | 2 | 1 | 1 | .. | .. | 1 | .. | 1 | .. | .. | .. | 1 | .. | 5 | .. | .. | 8 | 3 |
| 2 L | 2 | .. | 4 | .. | .. | .. | .. | .. | .. | .. | 1 | 1 | .. | 4 | .. | 3 | 6 | .. |
| 3 R | 1 | .. | 5 | .. | .. | 2 | .. | .. | .. | 1 | .. | .. | 1 | 7 | .. | .. | 4 | 2 |
| 3 L | 1 | .. | 9 | .. | .. | 1 | 1 | 1 | .. | .. | 1 | .. | 2 | 7 | .. | .. | 4 | 4 |
| 4 R | 2 | 1 | 8 | 1 | .. | 2 | .. | .. | .. | 1 | .. | 2 | .. | 6 | 1 | 1 | 8 | 2 |
| 4 L | 1 | 1 | 4 | .. | .. | .. | .. | .. | .. | 1 | .. | .. | 1 | 9 | .. | .. | 8 | 5 |
| 5 R | 1 | 1 | 3 | 1 | .. | .. | .. | 2 | .. | .. | .. | 2 | .. | 6 | .. | 5 | 6 | 2 |
| 5 L | 1 | 1 | 3 | .. | 1 | 1 | .. | .. | .. | .. | 1 | 1 | .. | 8 | .. | 1 | 6 | 3 |
| 6 R | 1 | 1 | 4 | 1 | .. | 5 | .. | .. | .. | .. | .. | 4 | .. | 8 | .. | .. | 4 | 4 |
| 6 L | 1 | 1 | 3 | .. | .. | 3 | .. | .. | .. | .. | .. | .. | .. | 8 | 2 | .. | 6 | 1 |
| 7 R | 1 | .. | 6 | .. | 2 | 4 | .. | .. | 1 | .. | .. | 1 | 1 | 7 | 1 | 5 | 7 | 5 |
| 7 L | 2 | .. | 3 | .. | .. | 2 | .. | .. | .. | 2 | .. | 1 | .. | 5 | .. | .. | 6 | 1 |
| | 1 Sup. glut. | | | | | | | | | | | | | | | | | |
| 8 R | 2 | 1 | 7 | .. | .. | 2 | .. | .. | .. | 2 | .. | .. | .. | 6 | 3 | 1 | 7 | 1 |
| 8 L | 2 | 2 | 8 | 1 | .. | 1 | .. | .. | .. | 1 | .. | 2 | .. | 8 | .. | 7 | 7 | 2 |
| 9 R | 1 | 1 | 4 | .. | .. | 3 | .. | .. | .. | .. | .. | .. | .. | 5 | .. | .. | 6 | 4 |
| 9 L | 1 | 1 | 6 | .. | .. | 2 | .. | .. | .. | 2 | .. | .. | 2 | 6 | 1 | 1 | 7 | 3 |
| 10 R | 2 | 1 | 6 | .. | 1 | 1 | .. | .. | 1 | 1 | .. | .. | .. | 9 | .. | .. | 5 | 1 |
| 10 L | 1 | 2 | 6 | .. | .. | 4 | .. | .. | 3 | .. | .. | .. | .. | 4 | .. | 2 | 5 | 1 |
| 11 | 1 | 2 | 2 | 1 | .. | .. | 1 | .. | .. | .. | 1 | .. | .. | 2 | .. | .. | 2 | .. |
| 12 | 3 | 3 | 8 | .. | .. | 1 | .. | .. | .. | 1 | .. | .. | 1 | 3 | 1 | 4 | 4 | .. |
| 13 | 2 | 1 | 2 | .. | .. | 1 | .. | 1 | .. | .. | .. | 1 | .. | 4 | .. | 2 | 6 | .. |
| 14 | 1 | .. | 4 | .. | .. | 3 | .. | .. | .. | 1 | .. | .. | 1 | 3 | .. | 2 | 2 | 2 |
| 15 | 1 Pud. | 1 | 9 | .. | .. | 2 | 1 | .. | .. | .. | .. | .. | .. | 10 | .. | .. | 5 | 1 |
| 16 | .. | 1 | 6 | .. | .. | 1 | .. | .. | .. | .. | 1 | .. | .. | 11 | .. | 1 | 7 | .. |
| 17 | 1 | 1 | 4 | .. | .. | 1 | .. | .. | .. | .. | .. | .. | 1 | 4 | .. | 3 | 7 | 2 |
| 18 | .. | 1 | 5 | .. | .. | 1 | .. | .. | 1 | .. | .. | .. | .. | 5 | .. | 1 | 6 | 2 |
| 19 | 1 | 2 | 14 | .. | .. | 4 | .. | 1 | .. | 1 | .. | .. | .. | 3 | .. | 2 | 13 | 2 |

* In this table, and in table 2, C. Fib. indicates circumflex fibular artery; Cruc., crucial anastomosis; Gen., genicular arteries; Inf. glut., inferior gluteal artery; Musc., muscular branches; Perf., perforating system of arteries; Peron., peroneal artery; Post. tib., posterior tibial artery; Pop., popliteal artery; Pud., internal pudendal artery, and Sup. glut., superior gluteal artery.

TABLE 2.—*High Division of the Sciatic Nerve*

A. Buttock and Thigh

| Specimen Number | Sciatic | | | | Medial Popliteal | | | Lateral Popliteal | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Buttock | | Thigh | Buttock | | Thigh |
| | Sup. Glut. | Inf. Glut. | Cruc. | Perf. | Inf. Glut. | Cruc. | Perf. | Inf. Glut. | Cruc. | Perf. |
| 20 R | .. | 1 | 1 | 2 | .. | .. | 2 | .. | .. | 1 |
| 20 L | .. | 1 | 1 | .. | .. | .. | 2 | .. | .. | 1 |
| 21 R | .. | 3 | 2 | .. | .. | .. | 5 | .. | .. | 2 |
| 21 L | .. | 2 | 1 | .. | .. | .. | 1 | .. | .. | 1 |
| 22 | .. | .. | .. | .. | 1 | .. | 4 | 2 | 2 | 4 |
| 23 | .. | .. | .. | .. | .. | 1 | 5 | 1 sup. glut. | .. | 5 |
| 24 | .. | .. | .. | .. | 3 | .. | 7 | 3 | .. | 4 |
| 25 | .. | .. | .. | .. | 2 | 1 | 9 | 1 | .. | 6 |
| 26 | .. | .. | .. | .. | 1 | 1 | 1 | 1 | 1 | 1 |
| 27 | 1 | 1 | .. | .. | .. | 1 | 3 | .. | 2 | 1 |
| 28 | .. | .. | .. | .. | 1 | 3 | 2 | 1 | 3 | 2 |

B. Popliteal Fossa and Leg

| Specimen No. | Medial Popliteal | | | | | | | Lateral Popliteal | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Popliteal Fossa | | | | Leg | | | Popliteal Fossa | | | Neck of Fibula | Leg | |
| | Pop. | Gen. | Musc. | Perf. | Post. Tib. | Peron. | Musc. | Pop. | Gen. | Musc. | C. Fib. | Anterior Tibial | Musculocutaneous |
| | | | | | | | | | | | | Ant. Tib. | Ant. Tib.-Peron. |
| 20 R | 1 | 1 | .. | .. | 5 | .. | 2 | .. | 1 | 3 | 1 | 15 | 4 |
| 20 L | 1 | .. | .. | .. | 5 | .. | .. | .. | 1 | .. | 1 | 5 | 1 |
| 21 R | 1 | .. | .. | .. | 3 | 5 | .. | .. | 1 | .. | 1 | 5 | 3 |
| 21 L | 1 | 2 | .. | .. | 9 | 2 | .. | .. | .. | .. | .. | 7 | 2 |
| 22 | 1 | .. | .. | .. | 8 | .. | 2 | .. | .. | 3 | 1 | 9 | 1 |
| 23 | 4 | .. | .. | .. | 5 | .. | 1 | .. | .. | .. | 1 | 6 | 1 |
| 24 | 1 | .. | .. | .. | 2 | .. | 2 | .. | .. | .. | 1 | 5 | 2 |
| 25 | 2 | .. | 2 | .. | 7 | .. | .. | 1 | .. | 1 | .. | 4 | 3 |
| 26 | .. | .. | 1 | .. | 2 | 1 | 1 | .. | .. | .. | 1 | 9 | .. |
| 27 | 2 | .. | .. | .. | 4 | .. | .. | .. | 1 | .. | .. | 3 | .. |
| 28 | 1 | .. | 1 | .. | 4 | 4 | .. | .. | .. | 1 | 1 | 5 | 4 |

muscles of the hip. According to Tonkoff,[9] this artery in most cases sends a twig to the nerve immediately it enters the buttock and another at the level of the ischial tuberosity, though on occasions he traced several (three to four) nutrient vessels of approximately the same caliber to the nerve. Haller [2] also described two nutrient arteries and Sappey [12] several nutrient arteries from this source, while Rauber [12] stated that muscular branches to the hamstring and adductor muscles provide nutrient vessels which accompany the nerve to the lower part of the thigh.

*Crucial Anastomosis.*—In the neighborhood of the quadrantus femoris muscle a supplementary and important supply (one to six nutrient arteries) was provided in most specimens by the arterial channels forming the crucial anastomosis. Owing to the dimensions of the anastomosis, it was not always possible to ascertain with accuracy the particular component from which the nutrient supply was obtained. On the evidence available, however, it was concluded that in the majority of the specimens the supply was provided by the medial femoral circumflex artery; the next most frequent source was the ascending branch of the first perforating artery, and only rarely did the supply come from the lateral femoral circumflex artery. The nutrient arteries from this system approached the nerve from its medial, lateral and deep aspects.

Henle [5] described a supply from the medial femoral circumflex artery but stated that the nutrient arteries recorded by other investigators as coming from the lateral femoral circumflex artery were not seen by him. Bartholdy [8] claimed that the nerve is frequently supplied by the medial femoral circumflex and only seldom from the lateral femoral circumflex artery. A supply from the medial femoral circumflex artery was recorded by Tonkoff [9] in 9 out of 10 specimens.

*Superior Gluteal and Internal Pudendal Arteries.*—Nutrient arteries were also observed coming from the superior gluteal and internal pudendal arteries, but reference to the tables will indicate the rarity of such a supply. Hyrtl [4] and Bartholdy [8] both recorded a supply from the latter artery.

### THIGH

In the thigh the nerve was constantly vascularized by one or more of the perforating arteries or from the anastomotic chain which these vessels outline on the posterior surface of the adductor magnus muscle (fig. 2). Some of the largest nutrient arteries observed passing to the sciatic nerve were derived from this system. They varied from one to fourteen in number, and the direct type predominated. It was uncommon to see long stretches of the nerve in the thigh without an entering nutrient artery. No distinction has been drawn between the various perforating arteries, since none predominated in supplying the nerve and frequently the nutrient arteries were derived from the anastomotic chain outlined by them. The nutrient arteries from this system commonly approached the nerve from its anterolateral aspect, though occasionally large muscular branches perforated the nerve en route to their destination.

Fig. 2.—Illustration of a dissection, showing the blood supply to the sciatic nerve from the inferior gluteal artery, crucial anastomosis and, in particular, the perforating anastomotic chain. The nerve has been displaced medially to demonstrate the latter.

A supply from the perforating arteries was recorded by Hyrtl [4] (second or third), Henle,[5] Quénu and Lejars [7] and Bartholdy.[8] Tonkoff

described a constant nutrient artery from the first perforating artery by way of a muscular branch to, what he calls, the triceps muscle—in 6 out of his 10 specimens two nutrient arteries reached the nerve from this source. In only 2 of 10 specimens did he find the nerve receiving a supply from the second perforating artery.

### POPLITEAL FOSSA

On entering the popliteal fossa the blood supply of the sciatic nerve or its popliteal branches was taken over by the popliteal artery and its branches. At the upper angle of the fossa they occasionally received a supply from the last perforating artery or from muscular branches of the femoral artery which had pierced the adductor magnus muscle. In the fossa the nutrient arteries may enter any aspect of the nerve or its divisions.

The medial popliteal nerve is intimately related to the popliteal artery, a fact which accounts for the high incidence of direct nutrient arteries from this source. Additional vessels were traced into the nerve from muscular and musculocutaneous branches of the popliteal artery and on occasion from the superior genicular system.

The lateral popliteal nerve, on the other hand, diverges from the artery as it descends to reach the neck of the fibula. For this reason its nutrient arteries were usually derived from more adjacent vessels, as represented by the muscular, cutaneous, musculocutaneous and superior lateral genicular branches of the popliteal artery. Failure of the nerve to establish a close relationship with a major arterial channel was also reflected in the large number of specimens in which no arteriae nervorum, or a single vessel only, reached the lateral popliteal nerve in the fossa.

Previous investigators have reported nutrient arteries reaching the popliteal nerves from the following sources: popliteal artery (Haller,[2] Walter,[3] Henle,[5] Bartholdy,[8] Tonkoff [9] and Portal [11]); medial and lateral sural and superior lateral genicular arteries (Hyrtl,[4] Bartholdy [8] and Tonkoff [9]); musculocutaneous branch of the popliteal and muscular branches from the femoral artery which had passed through the adductor magnus muscle (Tonkoff [9]).

*Posterior Tibial Nerve.*—In the posterior compartment of the leg the posterior tibial nerve and artery are closely bound together. It is therefore not surprising to find the nerve constantly receiving a large number (two to eleven) of small nutrient twigs directly and at frequent, though irregular, intervals along its course. An additional supply was provided by the peroneal artery and, indirectly, by the muscular branches of the two aforenamed vessels.

In the distal third of the leg it was by no means uncommon to see the tibial nerve perforated by the main arterial channel or one of its large branches (in 8 out of 40 specimens).

Tonkoff [9] alone has given a detailed account of the blood supply of this nerve. He stated that the nerve customarily receives a nutrient branch from the peroneal artery not far from its origin and four to five from the posterior tibial artery. When the latter artery was not developed, the nutrient twigs were said to come from the peroneal artery and its muscular branches. According to him, the number of nutrient arteries in the lower half of the leg exceeds that in the upper half, and this observation was confirmed in the present investigation. Bartholdy [8] found the nerve to be profusely supplied as far as the malleolus by the posterior tibial artery.

*Lateral Popliteal Nerve.*—At the point where the nerve is related to the neck of the fibula it was accompanied by the circumflex fibular artery, which frequently provided one or two arteriae nervorum in this situation—usually one entered the nerve where it was dividing into its superficial and deep divisions.

The musculocutaneous division was supplied in the interval between the peroneus muscles and the extensor digitorum longus muscle by large muscular arteries.

The anterior tibial nerve was supplied by the anterior tibial artery in the anterior compartment, where the intimacy of the neurovascular relationship was reflected in the large number (two to thirteen) of small nutrient arteries which the nerve received at frequent, but irregular, intervals. As in the case of the posterior tibial nerve, the majority of the nutrient vessels were of the direct type, though a large number of the indirect type were observed passing to the nerve in the following manner: As the artery descended, it usually gave off many transverse muscular branches to the extensor hallucis longus muscle. As these crossed the nerve transversely on their way to their destination (here the nerve is usually interposed between the muscle and the artery), they frequently gave a nutrient vessel to the nerve.

In the malleolar region the nerve was also occasionally supplied by the perforating peroneal artery (one nutrient in 1 specimen and two in another) and the anterior medial malleolar artery

(one branch in 2 specimens)—these are not listed in the tables.

A nutrient supply to the nerve in the region of the neck of the fibula has been described by Hyrtl [4] (fibularis branch of the anterior tibial artery) and Tonkoff [9] (ascending nutrient artery of the recurrent tibial artery). This would correspond to the supply which in the present investigation was observed coming from the circumflex fibular artery.

Bartholdy [8] reported indirect nutrient arteries to the superficial peroneal nerve from muscular branches of the anterior tibial artery, while a supply from this source to the anterior tibial nerve was mentioned by Haller,[2] Hyrtl [4] and Bartholdy.[8] A supply to the anterior tibial nerve from the anterior medial malleolar artery was reported by Bartholdy.[8]

## SUMMARY

In this report on the blood supply of the sciatic nerve and its popliteal divisions, attention is directed in particular to the disposition of the fasciculi and related nutrient vessels of the lateral popliteal nerve at the neck of the fibula. The relative susceptibility of this nerve to pressure is discussed on the basis of these observations.

The topographic features of the blood supply to the sciatic nerve and its divisions in the buttock, thigh, popliteal fossa and leg are described in detail.

University of Melbourne.

# STUDIES ON CEREBRAL EDEMA

## II. REACTION OF THE BRAIN TO EXPOSURE TO AIR; PHYSIOLOGIC CHANGES

M. PRADOS, M.D.; B. STROWGER, M.A., AND W. FEINDEL, M.D.
MONTREAL, CANADA

Our previous studies have shown that when one area of the hemisphere of the cat brain has been exposed to the air for a few hours after the dura has been opened, an acute reaction takes place. It was found that although this reaction is more pronounced in the exposed area, more remote regions in both hemispheres, as well as the subcortical structures, are also affected.

The pathologic changes in the reaction of the brain tissue have been described.[1] In its earliest phases a vasodilatation takes place, which reaches its maximum about two hours after the beginning of the exposure; by that time the pulsations of the brain disappear, and a certain degree of cerebral swelling may be noticeable. Intravenous injection of trypan dyes given immediately after the exposure reveals an increase in the permeability of the blood-brain barrier, as shown by the diffuse staining of the brain with the trypan solutions, due to the leakage of the dye through the capillary endothelium into the intercellular spaces. Microscopic examination of the brain shows morphologic changes in the vessels; capillaries are collapsed and empty or dilated and engorged; some show aneurysm-like dilatations; others have their walls broken, and actual hemorrhages are seen. There is widespread diapedesis in both the gray and the white matter, and the perivascular spaces are distended. With the benzidine stain areas of ischemia are evident, being more marked in the exposed area than in the rest of the brain. Neuronal changes are seen very early, and they are characterized either by swelling, chromatolysis and liquefaction or shrinkage and homogenization with dilatation of the perineuronal spaces. Microglial cells show moderate and brief mobilization. After forty-eight hours, the histopathologic picture begins to return to normal, and at the end of the third or fourth day the preoperative picture is almost reestablished. We concluded that the whole picture could be considered as a mild, edema-like reaction due to a primary alteration, both functional and anatomic, of the integrity of the circulation, the cellular alterations being secondary to the circulatory changes.

In the present studies we shall describe some of the physiologic changes observed in our animals as the result of the exposure. They include changes in the electrical activity of the cortex, changes in the $p_H$ of the exposed cortex and changes in permeability of the capillaries.

### MATERIAL AND METHODS

*Technic of Recording.*—The technic [1] of the exposure has been given in detail in our previous paper. The present studies were also made on cats, a total of 40 animals being used. Electroencephalograms were taken before and at varying times, from five hours to thirteen days, after operation. Most of our electroencephalograms were taken with the animal under anesthesia induced with pentobarbital sodium. Others, however, were taken with the use of curare or on the unanesthetized animal. When the animal was anesthetized, three fourths of the full dose of the anesthetic was given intraperitoneally, and the electroencephalogram was recorded one and one-half hours later in order to obtain the greatest similarity in the records. The curare [2] was given intramuscularly, and records were taken once the maximum degree of paralysis was obtained.

The technic used with the unanesthetized animal was similar to the method described by Rheinberger and Jasper.[3] Fine silver electrodes, made of wire 0.5 mm. in diameter, were rounded to a small ball on one end by heating and were insulated, except for the extreme end, with rubber coating. Insertion of the electrodes was carried out with the cat under surgical pentobarbital sodium anesthesia and with strict aseptic precautions. After reflection of the skin and subcutaneous tissues, straight-sided burr holes (1.5 mm. in diameter) were made through the skull. Care was taken not to injure the dura. The rounded ends of the silver wires were inserted through the holes to the surface of the dura and secured with sterile wooden wedges, which were then cut flush with the surface of the skull. The electrodes were so placed that one overlay the frontal, the central and the occipital region each of both hemispheres. All wires were led posteriorly and fastened in one or more

From the Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute.

1. *Prados, M.; Strowger, B., and Feindel, W.:* Studies on Cerebral Edema: I. Reaction of the Brain to Air Exposure; Pathologic Changes, Arch. Neurol. & Psychiat. **54**:163 (Sept.) 1945.

2. A brand marketed by Burroughs Wellcome & Co., Inc., and Intocostrin (E. R. Squibb & Sons) were employed.

3. Rheinberger, M. B., and Jasper, H.: Electrical Activity of the Cerebral Cortex in the Unanesthetized Cat, Am. J. Physiol. **19**:186, 1937.

places to the muscle sheath, and the skin was then sutured. The cats did not show any disturbance from these attachments. The following day electroencephalograms were taken by soldering the ends of the silver wires to wire leads and connecting to the recording machine.

In the anesthetized or the curarized animal the electrodes were placed on the scalp. The head was shaved, and silver chloride–felt electrodes were fastened to the skin with collodion, contact being secured by means of electrode jelly. The electrodes were placed over the areas corresponding to the regions of the skull in which the electrodes were inserted in the unanesthetized animal, so that in all experiments we could compare the same cortical regions. The electrodes were connected to a four channel, ink-writer amplifier in such a manner that the central electrode of each side was shared in common with the frontal and the occipital electrode of the same side. The records were taken with the animal resting on a cushioned box in an electrically shielded, dark, sound-proofed room, with the recording system in an adjacent room.

Because of the individual differences of the electrical activity of the brain in our animals, preoperative records were taken in each experiment. Most of the preoperative records were taken one or more days preceding the operation; a few, however, were obtained immediately before the exposure. Sample elctroencephalographic tracings were taken at various gains so that direct comparison with the postoperative records at their optimum gain could be made. Postoperative records were taken on some animals on the second, fourth and sixth days after operation and on others on the first, third and fifth days. Some of the records were taken even on the seventh and ninth days; only 1 was taken on the thirteenth day after the exposure.

*Studies of $p_H$.*—Four acute experiments were carried out on cats in which the $p_H$ of the exposed cortex was determined continuously over periods of four hours. The apparatus used was a modification of that previously described by Dusser de Barenne and associates. Glass electrodes filled with silver acetate were made according to the method described by Nims [4] and, with a silver chloride-saline solution wick electrode, were placed on the pial surface of the cortex and used in conjunction with a modified form of the microvoltmeter of Burr, Lane and Nims, a Leeds and Northrup Type K Potentiometer and a Leeds and Northrup Galvanometer No. 2420. The electrodes were calibrated immediately before each experiment against one-fifteenth molar phosphate buffer standard. Voltages were read off directly from the potentiometer at five to ten minute intervals during the exposure and changed to $p_H$ readings with use of the calibration curve. The glass electrode leading to the microvoltmeter was shielded. The exposures were made in the usual manner employed with cats under pentobarbital sodium anesthesia, but with some care to maintain the temperature of the surroundings as constant as possible.

The anatomic position of the electrodes on the cortex in all cases was either the lateral gyrus or the middle suprasylvian gyrus. The direct current potential gradings were not recorded but may be neglected in an estimation of the $p_H$ to 0.05 unit; and throughout any one experiment they were stable enough to admit more accurate measurement. Variations in temperature of the surface of the cortex would bring the total estimated experimental error for the $p_H$ to 0.1. Only the shifts in $p_H$ values which were greater than the experimental error are mentioned as significant.

*Studies of Permeability.*—Intravenous injections of solutions of trypan dyes were used to determine the degree of permeability of the capillary endothelium. Trypan red or trypan blue was used in a 1 per cent aqueous solution, of which 20 cc. was injected intravenously at the end of the exposure and on the following day. The animal was killed thirty-six hours after the exposure. In a series of animals, adrenal cortex extract was given intramuscularly in a dose of 1 to 2 cc. per kilogram of body weight. One injection was given one and one-half hours before opening the dura; a second injection, at the end of the exposure, after the wound was closed, and a third, twenty-four hours after the first, about four hours before killing the animal. In 2 animals the adrenal cortex extract was sprayed over the exposed cortex by means of an atomizer at one hour intervals during the exposure. In most of our experiments we used the commercial preparation of the Connaught Laboratories, Toronto. In others we used an extract specially prepared by the Frosst Laboratories, Montreal. We used also a preparation offered to us by Dr. Kendall. In another series of cats we injected preparations of the anterior lobe of the pituitary made under Dr. Collip's supervision in the Research Institute of Endocrinology, McGill University. We used two preparations. First, we employed a diluted extract, of which 10 cc. was injected intraperitoneally each day over a period of five to eight days before the exposure. In other experiments we injected a single dose two hours before the exposure. We also used a special concentrated extract prepared by Dr. A. H. Neufeld [5] in Dr. Collip's laboratories according to the technic published by him. After many trials, we found that the dose of 1 mg. per kilogram of body weight, injected subcutaneously the day before the exposure in two or three fractionated doses, was the most adequate.

For these two series of animals treated with glandular preparations, electroencephalograms were recorded in the usual manner except in the experiments with trypan dyes, in which no electrical activity was recorded.

## RESULTS

*Normal Electroencephalogram of the Cat.*—Our records for the unanesthetized animal, as well as for the curarized cat, were similar to those described by Rheinberger and Jasper.[3] These records were characterized by waves of very low amplitude and high frequency followed by long or short periods of high amplitude and slow frequency. This type of electroencephalogram is very similar to that found for man during sleep. These bursts of high amplitude and slow frequency were more noticeable in the frontocentral regions than in the more posterior areas and possibly represented synchronized potentials originating in the motor cortex (figs. 2 to 7 inclusive).

For the anesthetized animal, with scalp electrodes, the type of electroencephalogram varied

4. Nims, L. F.: Glass Electrodes and Apparatus for Direct Readings of $p_H$ in Vivo, Yale J. Biol. & Med. **10**:241, 1938.

5. Neufeld, A. H.: Preparation of the Pituitary Corticotrophic Hormone, Proc. Soc. Exper. Biol. & Med. **54**:90, 1943.

somewhat. It was characterized by bursts of potentials of an amplitude ranging from 10 to 20 microvolts and a frequency of 15 cycles per second. These bursts had a duration of two to three seconds and occurred every five to eight seconds. Between these bursts were seen slow waves of a much lower amplitude, with a frequency of 4 to 5 cycles per second, on which potentials of much higher frequency and lower amplitude were superimposed. As a rule these bursts were bisynchronous; that is, they occurred simultaneously in all leads in both hemispheres. Sometimes, however, one hemisphere showed them a few tenths of a second before they appeared on the opposite side. The records of the occipital regions consistently showed a lower amplitude than those of the frontoparietal region. A certain dominance of the right hemisphere over the left was frequently observed. The number of bursts per minute, as well as their amplitude, changed with the depth of the anesthesia.

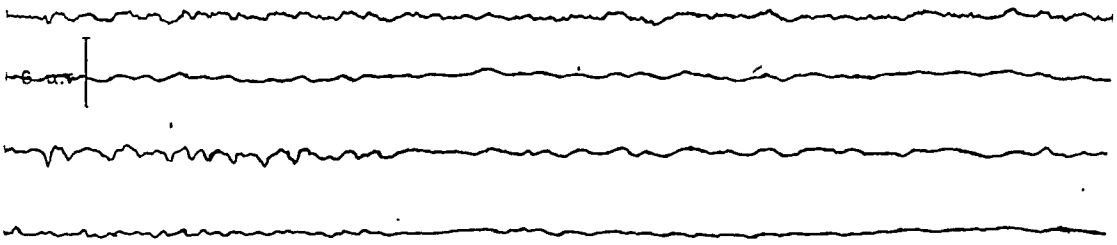


Fig. 1.—Electroencephalogram of the cat twenty-four hours after exposure. See text.

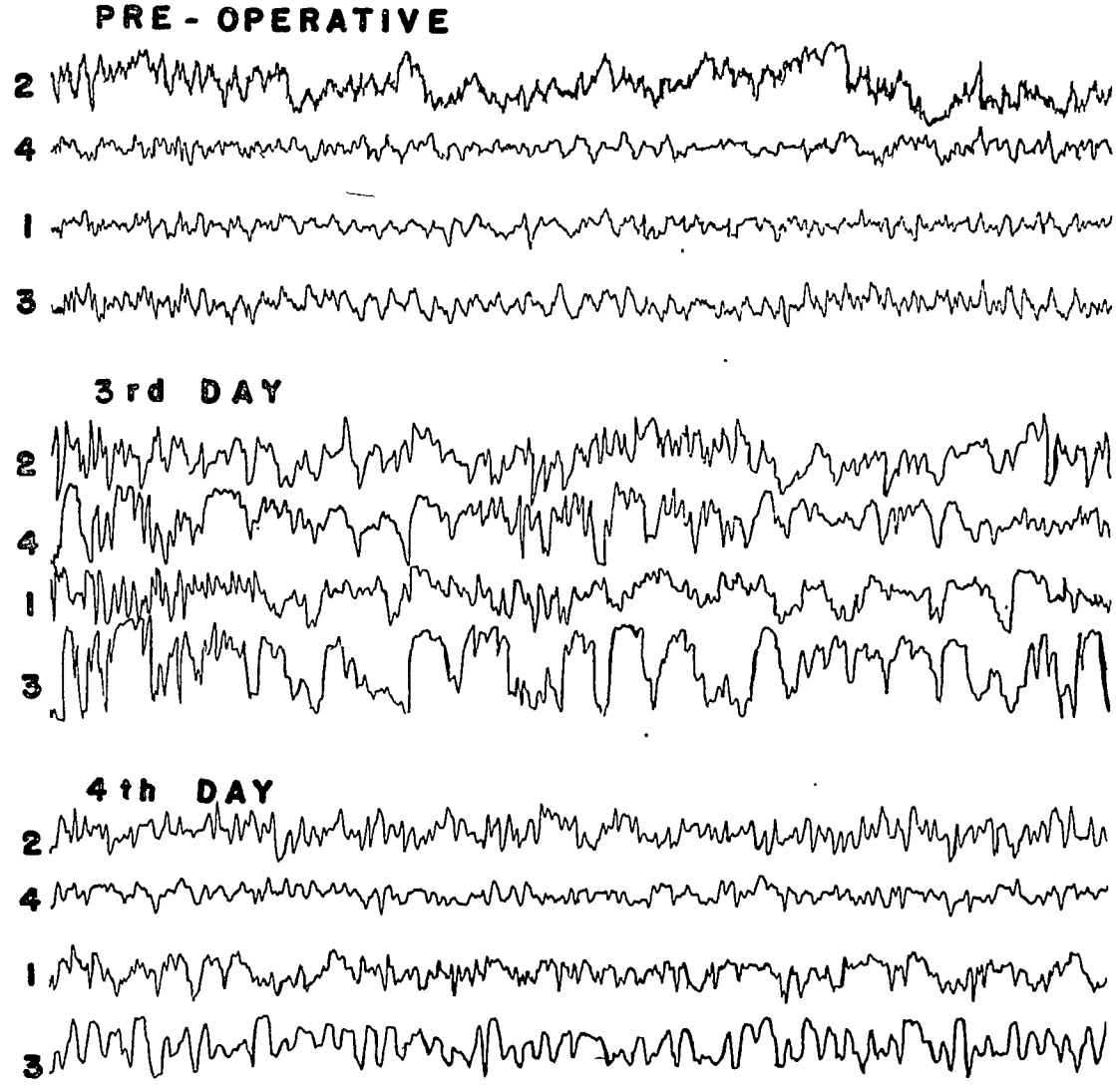



Fig. 2.—Changes in the electroencephalogram of the cat on the third and fourth days after exposure. Leads 2 and 4 are from the unexposed hemisphere; leads 1 and 3, from the exposed one.

*Effect of Exposure on the Electroencephalogram.* — The electroencephalogram recorded twenty-four hours after the exposure revealed a

considerable depression in the amplitude in all leads. The depression, which was always present at this time, varied somewhat from one experiment to another, and its picture differed in the unanesthetized animal, with dura leads, from that observed in the anesthetized cat, with scalp electrodes. With the latter the activity recorded in some cases was extremely low, and the record showed an almost flat line with random delta waves (fig. 1). With dura leads, however, the activity recorded consisted of extraordinarily fast waves of extremely low amplitude, although at times no activity at all was recorded. Occasionally, there were single bursts of potentials of higher amplitude and slow frequency.

On the third day the pattern of the electroencephalogram changed completely (fig. 2). There was a generalized increase in amplitude, which might be three or four times as great as that recorded before the operation. Sharp waves of a frequency of 6 to 7 cycles per second and slow waves of a frequency of 1½ to 3 cycles per second and an amplitude of 100 to 160 microvolts (scalp electrodes) were seen throughout the entire record, alternating at times with waves of much lower amplitude and frequency. Isolated typical spikes could also be seen, occasionally followed by one slow wave in a way identical with that observed during the epileptic discharge. With dura leads one found the same increase in amplitude, although here the difference between the postoperative and the preoperative record did not seem so dramatic. However, there was a definite increase in amplitude: the high ampli-

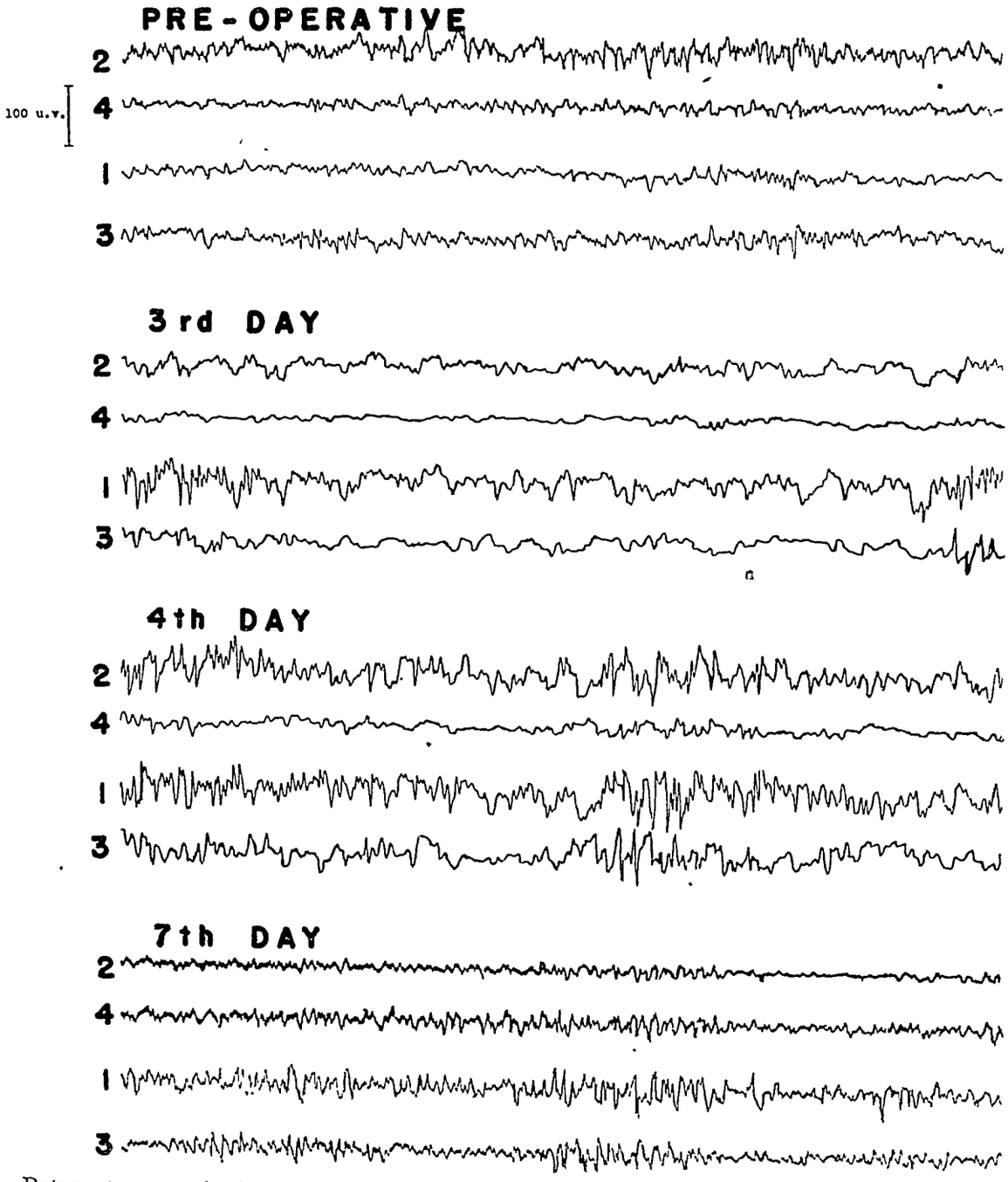



Fig. 3.—Return to normal of the electroencephalogram of the cat on the seventh day after exposure. Leads are as in figure 2.

tude and slow wave activity was not so marked and in some cases was seen only at random, and for many seconds only the high frequency activity might be recorded. Spikes were also seen.

The changes described could be seen in all leads, although the exposed side reacted more intensely than the unexposed one. We observed some correlation between the degree of swelling during the exposure and the intensity of these changes. Figures 2 and 3 show the electroencephalograms of 2 animals operated on at the same time. In 1 cat the swelling was extreme, and because of that the dura could not be closed. In this animal's record the changes are generalized and of the same type in all leads. In the case of the other animal, in which the swelling was not so marked, the picture is rather different. The parieto-occipital leads of both sides still show considerable depression, more pronounced, however, on the unexposed side. Random sharp waves can be seen in this lead, whereas in the exposed hemisphere the frontoparietal lead shows already the excitatory phenomena, but not so intensively as in the other animal.

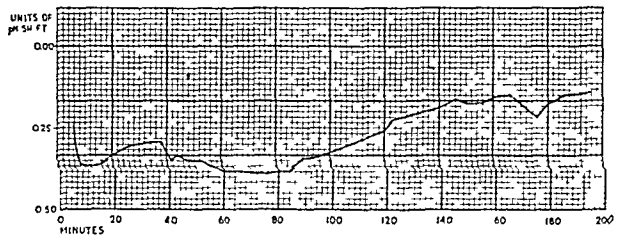



Fig. 4—Changes in $p_H$ of the cerebral cortex during the exposure See text.

Between the fourth and the fifth day these electroencephalographic signs began to subside. The amplitude showed a tendency to come back to the preoperative condition; the spikes and sharp waves practically disappeared, although the delta activity might still persist. About the seventh or ninth day the electroencephalogram usually resembled the preoperative record.

*Studies of the* $p_H$.—Determinations of the $p_H$ were carried out continuously over a period of four hours on the exposed cortex of 4 cats. The first half of the exposure period in 3 of our experiments was characterized by some fluctuation in the $p_H$ level but with a definite shift in the direction of alkalinity, which might appear early or not until the latter part of the second hour. During the second half of the exposure our records showed a continuously progressive decrease in $p_H$ values. In the fourth cat the shift to the acid side began almost immediately; but in this animal the recording was started some time after the actual operative exposure had been made, and there is no reason to believe it inconsistent with the other results. Figure 4 shows graphically the changes in 1 of our experiments, recorded over a period of two hundred minutes. After some fluctuations, lasting for fifty minutes, there was a definite, stable shift in the direction of alkalinity, which lasted less than half an hour. Eighty-five minutes after the beginning of the exposure one can see the continuously progressive shift to the acid side, as revealed by the decreasing $p_H$ values.

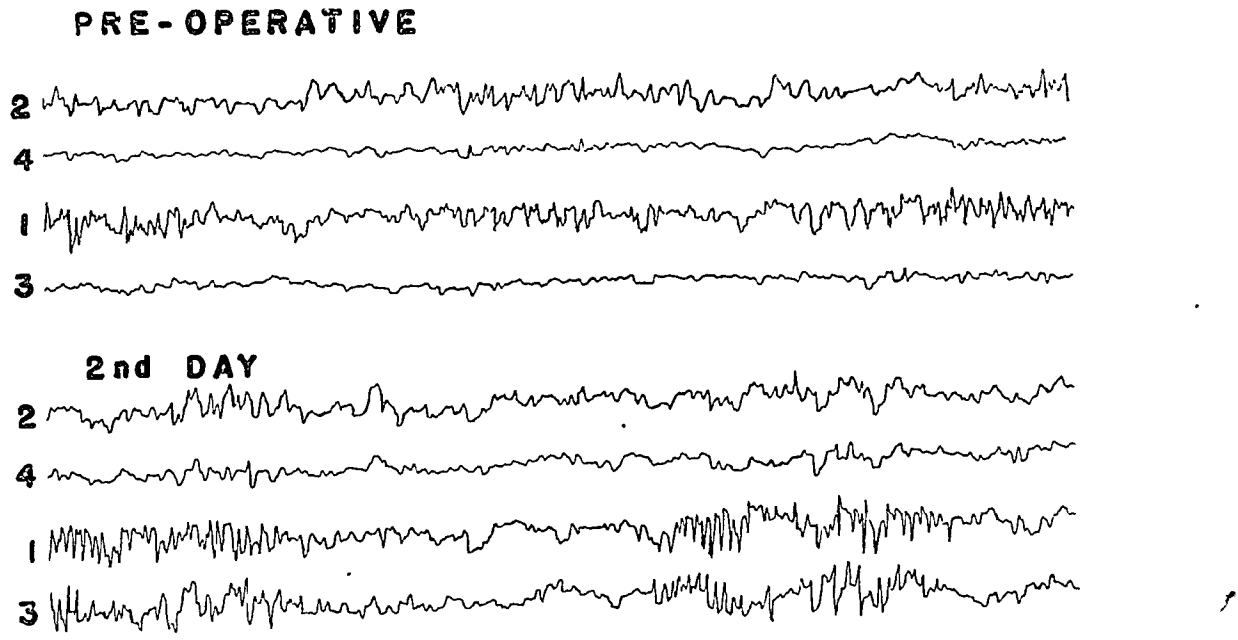



Fig 5—Effect of adrenal cortex extract on the electroencephalogram of the cat on the second day after exposure See text.

*Studies on Permeability.*—Our previous studies showed that when solutions of trypan dye are

injected intravenously into the animal after the exposure, the whole brain is stained by the acid dye, but the exposed area more deeply than the rest of the brain. In other words, the exposure produces an opening of the blood-brain barrier which allows the leakage of the dye through the capillary endothelium. Our pathologic studies have shown, also, that the capillaries of the brain undergo changes which are responsible for the outflow of fluid into the intercellular spaces.

in this type of experiment. The upper record shows the electroencephalogram of the animal before the exposure, and the lower record, the electroencephalogram two days after the exposure. The changes present are mild. On the unexposed side one can hardly detect any change either in the amplitude or in the pattern of the electrical activity. The exposed hemisphere shows a moderate hypersynchrony, which is particularly noticeable in the central-posterior region, but the

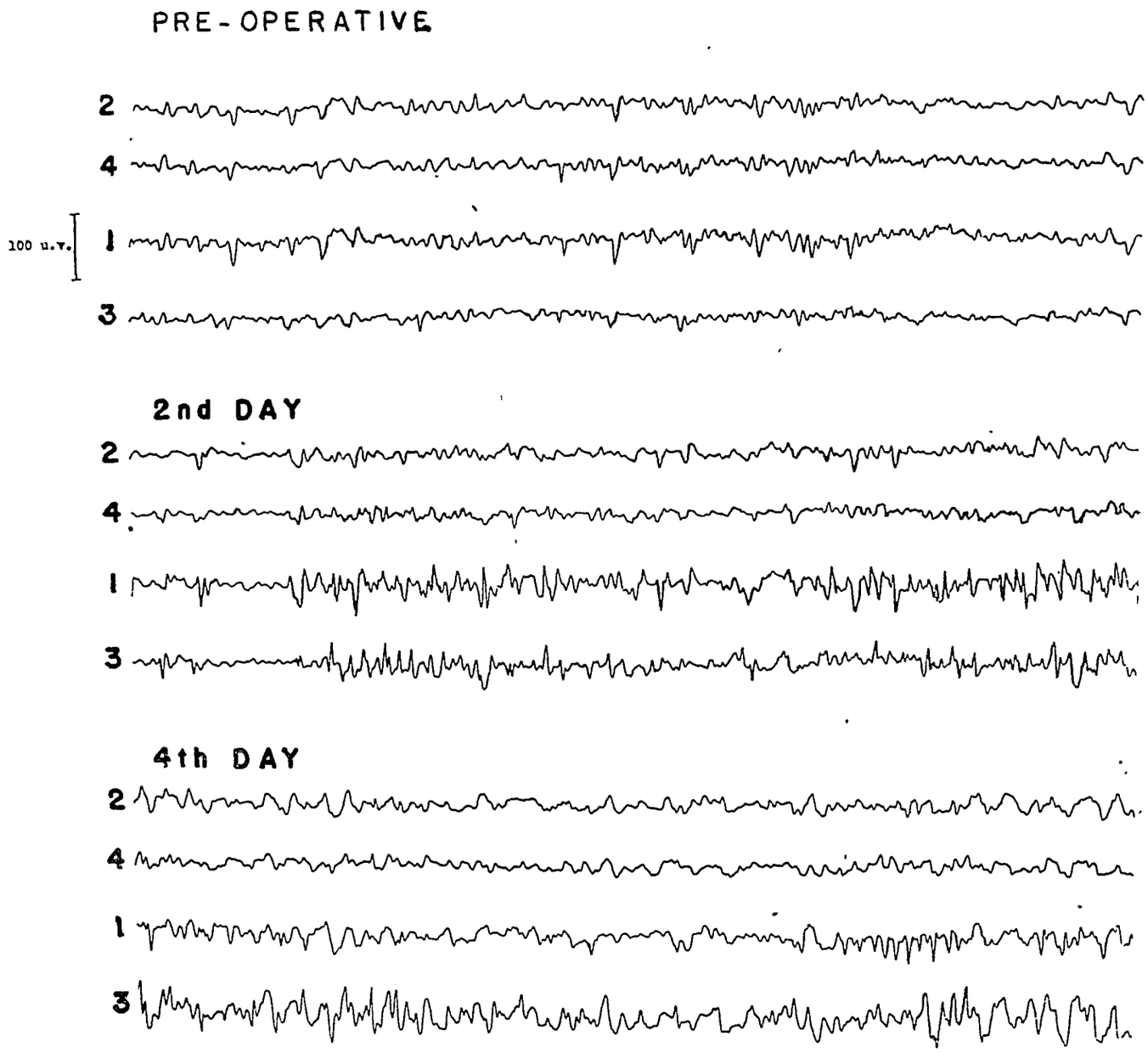



Fig. 6.—Effect of adrenal cortex extract on the electroencephalogram on the fourth day after exposure. See text.

We treated a series of animals before and after the exposure with injections of adrenal cortex extract and studied both the electroencephalographic changes and the behavior of the intravenously injected trypan solutions.

Effect of Adrenal Cortex Extract on the Electroencephalogram of the Exposed Brain: In a series of 10 cats we studied the effect of adrenal cortex extract on the electroencephalogram of the exposed brain. Figure 5 shows a typical record

increase in amplitude is low, the average amplitude being 80 microvolts, which represents an increase of only about 20 microvolts over that of the preoperative record. There are small numbers of single spikes or sharp waves.

In 2 animals the adrenal cortex extract was sprayed on the exposed area by means of an atomizer immediately after the opening of the dura and during the exposure. Electroencephalograms recorded on the second day after the ex-

posure showed only moderately increased amplitude in all leads of the exposed hemisphere; this increase in the record taken on the fourth day was practically limited to the posterior region of the same side (fig. 6).

In another series of 10 animals, we used a special preparation containing a high concentration of the corticotropic factor of the anterior lobe of the pituitary gland. The effect on the electroencephalogram was similar to that obtained when the adrenal cortex extract was employed. Figure 7 is the record of a typical experiment.

Effect of Adrenal Cortex Extract on Permeability of the Blood-Brain Barrier: Solutions of trypan blue were injected intravenously immediately after the end of the exposure into animals which previous to the operation had received adequate doses of adrenal cortex extract intramuscularly. Figure 8 shows the brains of 2 cats. In the case of the cat whose brain is shown in *A* the exposure was performed and the trypan blue injected but no adrenal cortex extract was given. The left hemisphere was exposed in both animals. In the case of the cat whose brain is shown in *B* the exposure was performed and the trypan blue injected in an identical manner except that 3 cc. of the adrenal cortex extract per kilogram of body weight was injected one and one-half hours previous to the exposure and three hours later. The control experiment (*A*) shows that the entire surface of the brain was tinged with the dye, although the staining was particularly intense in the exposed area of the left hemisphere. It can be noticed, also, that the exposed area is evidently swollen as compared with the rest of the brain, and the limits of the exposed area in the lateral and suprasylvian gyri can be detected by the degree of swelling. The surface of the brain in *B* shows a different picture. There is practically no staining at all with the trypan blue. Only in the posterior part of the lateral gyrus and a small patch in the posterior part of the suprasylvian gyrus can slight traces

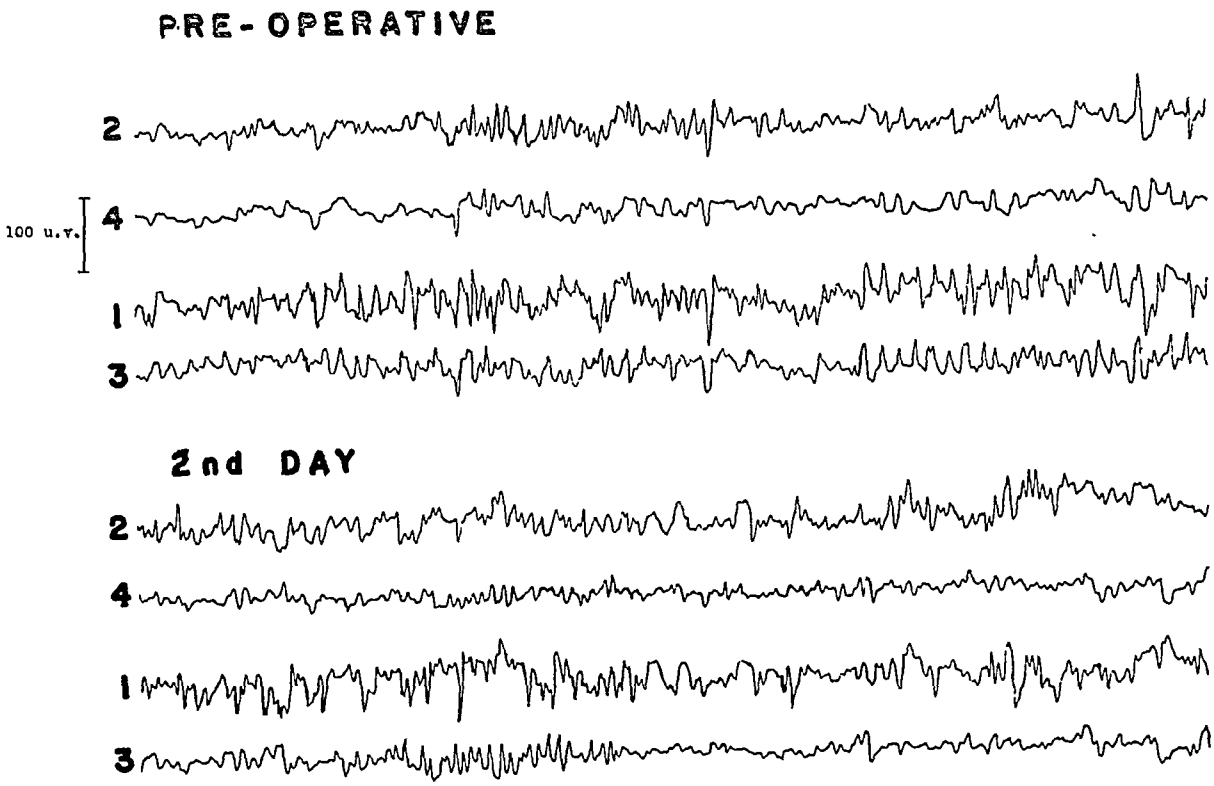



Fig. 7.—Effect of a preparation containing the corticotropic factor of the pituitary on the electroencephalogram. See text.

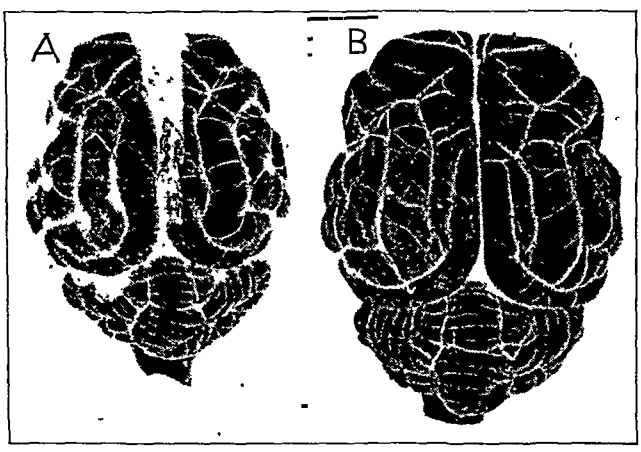



Fig. 8.—Brains of 2 cats in each of which the left hemisphere was exposed to the air for five hours and a solution of trypan blue was injected intravenously at the end of the exposure. In the cat whose brain is shown in *B*, adrenal cortex extract was injected intramuscularly during and after exposure. See text.

of the dye be seen. Moreover, no swelling of the exposed area can be seen at all. Figure 9 shows a coronal section of the brain of another animal. In *A*, which represents the control experiment, one can see that the cortex of the lateral gyrus is damaged as the result of the herniation of the brain substance through the wound in the bone, due to its swelling during the exposure. Of the cortical areas, the lateral and the suprasylvian gyrus, as well as the upper part of the sylvian gyrus, appear stained with the dye. The thalamus and other subcortical structures appear dark, especially when they are compared with the completely unstained section of the brain in *B*, which represents a section of the brain of the animal previously treated with the adrenal cortex extract.

The degree of efficiency of these glandular preparations in preventing the leakage of the dye through the wall of the vessels depends on the amount of the injected extract. We found the best responses in the cat when a dose of 2 cc. per kilogram of body weight was injected. This

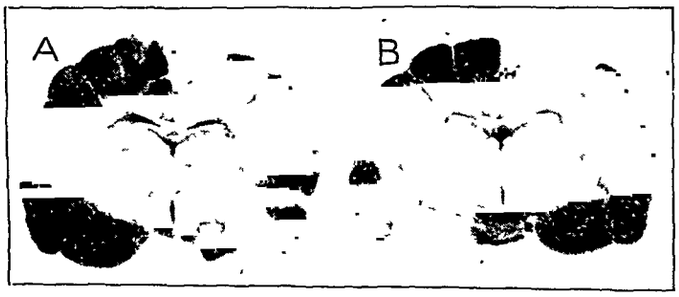



Fig. 9.—Coronal sections of the brains of 2 other cats, in an experiment similar to that illustrated in figure 8.

dose was repeated three, six and twenty-four hours after the exposure. An excessive dose seems to produce the opposite effect, especially when the preparation containing the corticotropic factor is used.

## COMMENT

The type of electrical potentials described is characterized by a relatively short period of marked depression of the cortical activity (low amplitude waves; flat record with random slow waves) followed by a stage of hyperirritability, as indicated by the increase in amplitude of all types of waves and the hypersynchrony, represented by the presence of bursts of large slow waves and the sharp wave or spike and slow wave activity. This picture is almost similar to that described by investigators in cases of an acutely damaged cerebral tissue and is interpreted by Jasper and Penfield [6] as the expression of a metabolic deficiency associated with neuronal hyperirritability. The sequence and type of the electrical changes are almost similar, also, to those described by Sugar and Gerard [7] in conditions of acute cerebral ischemia in the cat. These investigators demonstrated that there exists a comparable sequence of phenomena between the clinical symptoms and the electroencephalographic signs. After the stopping of the circulation in the brains of cats due to occlusion of both vertebral and carotid arteries, they observed first increased respiration, followed by general tonic and clonic movements, and then progressively diminishing breathing and movements, ending in apnea and flaccid areflexia. The brain potentials showed, typically in the motor cortex and with special variations in other cerebral areas, a rather constant pattern. High frequency waves appeared or increased in speed and amplitude. In twelve seconds all fast waves, and in twenty seconds the slower ones, had disappeared. The record remained flat for the rest of a twenty second period of anemia. Five minutes after restoration of the blood flow, electrical activity was ushered in by low, irregular waves with a spindle of 6 to 9 per second, gradually fading into a newly starting spindle of considerable regularity; fast waves soon appeared, partly superimposed on other spindles; in four to six minutes the normal activity was reestablished.

These electroencephalographic changes following acute cessation and reestablishment of the blood flow may be compared with our observations, which differ only quantitatively from the experiments of Sugar and Gerard. The pathologic studies carried out on the brains of our animals showed a rather constant sequence of circulatory changes. In fact, after a period of several hours from the beginning of the exposure, characterized by definite vasodilatation, an ischemic condition occurred, more noticeable in the cortex, which was obvious in twenty-four hours, precisely when the brain potentials showed the fast, low amplitude activity or simply a flat line with some delta waves. This period of relative ischemia lasts generally no longer than twenty-four hours and is followed by a relatively slow but progressive reestablishment of the circulation, in some areas earlier than in others, the exposed area being always more affected than the unexposed area. It is not until four or five days later that the circulation becomes rather normal, although areas of impaired blood supply can still be seen. During these stages, the brain potentials show a generalized increased ampli-

6. Jasper, H., and Penfield, W. G.: Electroencephalograms in Post-Traumatic Epilepsy, Am. J. Psychiat. **100**:365, 1943.

7. Sugar, O., and Gerard, R. W.: Anoxia and Brain Potentials, J. Neurophysiol. **1**:558, 1938.

tude, with bursts of slow waves of still larger amplitude and random sharp waves and spikes; this hypersynchrony indicates a condition of hyperirritability of the neurons, with the tendency to discharge in unison. This hyperirritability disappears long before the delta activity, which may persist for many days.

That impaired cerebral blood supply may produce neuronal hyperirritability was suggested by Penfield [8] on the basis of his studies on the circulation in the brain of epileptic patients. Further electroencephalographic studies carried out by Jasper and Penfield [6] lend support to this conception by the recording of spikes and sharp waves from the border zones of the meningocerebral cicatrix and the evidence of cessation of the epileptic attacks after adequate surgical removal of the scar.

It is interesting, also, to mention that coincidental with the circulatory changes in the brains of our animals and the appearance of the cerebral potentials described there were neuronal alterations, mainly of two types; first, acute cellular swelling and chromatolysis with eventual liquefaction or simple appearance of "ghost" cells and, second, homogenization and shrinkage of the neurons. Of these two types, the first was the most commonly seen during the twenty-four hours following the exposure, whereas the second was predominant in the ensuing days. This observation makes possible the suggestion that probably there exists some correlation between the morphologic alterations in the neurons and the type of potentials observed.

The small series of studies on the $p_H$ of the exposed cerebral area show that after a sudden and short shift in the direction of alkalinity of the brain a constant and progressive increase in acidity takes place, which is maintained during the entire time of exposure. We believe that the changes in the $p_H$ values are related also to the sequence of vascular changes occurring in the cortex.

The importance of local cerebral blood flow in the maintenance of a constant physiologic $p_H$ of the cortex has been demonstrated by Jasper and Erickson.[9] According to these investigators, an increase in blood flow produced by various means tends to increase the local $p_H$ of the cortex. On the other hand, if the local blood flow does not increase after excessive neuronal activity, as in metrazol discharge, an acidity is produced which will persist somewhat longer than when the local vasodilator mechanism is more adequate. It would seem reasonable, also, that if the local flow is excessively decreased, as in congestion, and is insufficient to care for the normal resting activities of the neurons, a condition of local acidity might tend to result.

The shift toward alkalinity observed in 3 of our experiments would seem to be related to the hyperemia of the exposed cortex seen during the earlier part of the exposure, when one would expect an increase in blood flow in the exposed area. Since the $p_H$ of arterial blood is usually somewhat greater than the local $p_H$ of the cortex, this increased local blood flow would tend to increase the local cortical $p_H$. The progressive shift to the acid side which follows seems also to be due to the vascular conditions of the exposed area, since at this time congestion of the cortical vessels is evident and it would appear that the local blood flow is insufficient to maintain adequately even the resting activities of this area. The accumulation of metabolites accompanying this congestion would explain the decrease in the $p_H$ of the cortex.

In our previous paper we have shown evidence that as a result of the exposure the capillary endothelium becomes more permeable. This allows not only an increased outflow of fluid into the interstitial spaces but the leakage of substances which in normal conditions are not permeable to the so-called blood-brain barrier. Our present studies show that adrenal cortex extract, either injected into the system or sprayed locally on the exposed cortex, has some protective effect on the brain potentials, preventing somewhat the depression of the first period and the subsequent excitatory phenomena. It also protects the capillary endothelium (if adequate doses of the extract are given) against the increased permeability which follows the exposure. This is demonstrated by the results of the trypan experiments, in which the brain remains unstained after the systemic injection of the dye solution.

At the present time considerable evidence indicates that the capillaries of the adrenalectomized animal are atonic, dilated and abnormally permeable. Menkin [10] showed that the leakage of trypan blue into extravascular spaces after the injection of leukotaxine could be reduced by either adrenal cortex extract or desoxycorticos-

8. Penfield, W. G.: Circulation of the Epileptic Brain, A. Research Nerv. & Ment. Dis., Proc. **18**: 605, 1938.

9. Jasper, H., and Erickson, T. C.: Cerebral Blood Flow and $p_H$ in Excessive Cortical Discharge Induced by Metrazol and Cortical Stimulation, J. Neurophysiol. **5**:333, 1941.

10. Menkin, V.: Effect of Adrenal Cortical Extract on Capillary Permeability, Am. J. Physiol. **129**:691, 1940.

terone. Freed and Lindner [11] found that while cortex extract and corticosterone would prevent leakage of dye after injections of leukotaxine or peptone, desoxycorticosterone was without positive effect. Shleser and Freed [12] found that the adrenal cortex extract retarded leakage of dye from the capillaries after injections of peptone but that the corticosterone was ineffective. Cope [13] demonstrated that after administration of adrenal cortex extract there is a change in capillary permeability, permitting the retention of plasma protein within the blood stream.

In our experiments the circulatory changes, with the edema-like reaction, following exposure were pronounced in the region of the hypothalamus (fig. 10). This is not surprising when one remembers that this region is extraordinarily rich in blood vessels and that its capillaries are much more permeable than those in the rest of the encephalon.[14] The circulatory and vascular changes in this region produced by virtue of the exposure may depress to some extent the activity of the anterior lobe of the pituitary, owing to a certain damage of the nerve centers of the hypothalamus. This eventually impairs the release in sufficient quantity of the corticotropic hormone necessary to activate the adrenal cortex in the condition of stress involved in the operative procedure and the exposure. We suggest this as a possibility in view of the fact that in our animals previously treated with a corticotropic preparation the changes in the potentials were slight, although some hypersynchronism could still be seen in the exposed area on the third or fourth day after exposure. The permeability of the capillaries was also partly maintained.

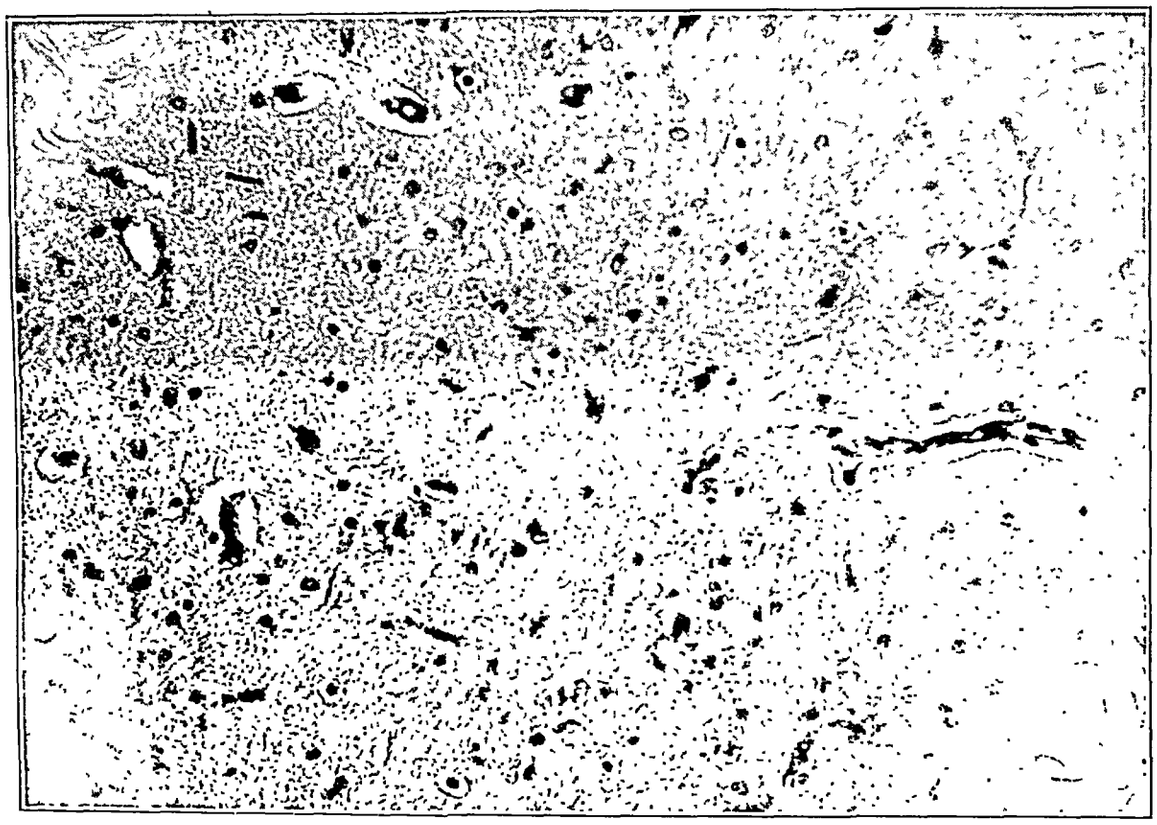


Fig. 10.—Edematous reaction of the hypothalamus of the cat twenty-four hours after the exposure.

The protective effects observed with the administration of adrenal cortex extract or a preparation containing the corticotropic factor of the anterior lobe could be explained either by the direct effect of the active principle of the adrenal cortex on the capillaries, which would keep their tonicity and permeability in good condition, or by the supposed beneficial action of the adrenal cortex extract in conditions of anoxia, as seems to have been demonstrated by various investigators.

In any case, we believe that the electrical changes described are due to an impairment in the metabolism of the brain tissue associated with hyperirritability of the neurons. The circulatory changes observed being primary to the electroencephalographic changes, we are inclined to accept the explanation that a condition of rela-

11. Freed, S. C., and Lindner, E.: The Effect of Steroids of the Adrenal Cortex and Ovary on Capillary Permeability, Am. J. Physiol. **134**:258, 1941.

12. Shleser, I. H., and Freed, S. C.: The Effect of Peptone on Capillary Permeability and Its Neutralization by Adrenal Cortical Extract, Am. J. Physiol. **137**:426, 1942.

13. Cope, O., cited by Swingle, W. W., and Remington, J. W.: The Role of the Adrenal Cortex in Physiological Process, Physiol. Rev. **24**:89, 1944.

14. Goldmann, E. E.: Vitalfärbung am Zentralnervensystem, Berlin, G. Reimer, 1913.

tive ischemia due to the transitory circulatory impairment accounts for the mechanism of the physiologic manifestations, as well as the pathologic picture observed as the result of the exposure.

Which factors determine these primary changes of the cerebral blood supply will need further investigations.

## SUMMARY AND CONCLUSIONS

When one area of the cat brain has been exposed to the air for a few hours some physiologic alterations take place. They include changes in the electrical activity of the cerebral cortex, changes in the $p_H$ of the exposed cerebral area and changes in the permeability of the capillary endothelium.

The electroencephalogram of the cat after the exposure shows a marked depression of the cortical activity, which lasts about twenty-four hours. This is followed by an excitatory state, characterized by a generalized increase in the amplitude and frequency of the cortical potentials and the presence of frequent bursts of large sharp and slow wave and spike activity. These excitatory phenomena slowly subside, and between the fifth and the seventh day the electroencephalogram returns to the preoperative condition.

The $p_H$ of the exposed cortex fluctuates somewhat during the first half of the period of exposure, but with a definite shift in the direction of alkalinity. During the second half of the exposure there is a continuously progressive decrease in the $p_H$ value.

Adrenal cortex extract and extracts of the anterior lobe of the pituitary containing the corticotropic factor protect the cortex against the electroencephalographic alterations elicited by the exposure. They also prevent the swelling of the brain and the changes in permeability of the cerebral capillaries which follow the exposure.

These physiologic changes are explained as the result of the described functional and morphologic changes in the cerebral circulation which take place from the beginning of the exposure.

1025 Pine Avenue West.
207 Leland Avenue, Menlo Park, Calif.
3801 University Street.

# Obituaries

## SMITH ELY JELLIFFE, M.D.
1866-1945

When Smith Ely Jelliffe died, on Sept. 25, 1945, American neurology and psychiatry lost a versatile and able exponent. His breadth of learning and culture and his enthusiasm for his life's work combined to form a well rounded scientist, an able medical editor and a teacher of distinction.

(Photographed by Blackstone Studios, 20 West Fifty-Seventh Street, New York)

SMITH ELY JELLIFFE, M.D.
1866-1945

Dr. Jelliffe was born in New York city on Oct. 27, 1866. Both his parents were school teachers, and his father was later principal of a public school in Brooklyn, where most of his early life was spent. He was graduated from public school and then attended the Brooklyn Polytechnic Institute, with the idea of becoming a civil engineer. This idea, however, did not long survive, for he soon learned that he hated mathematics. His main interest was in biology, especially botany, and it was only natural that he should drift toward medicine. In 1889 he was graduated from the College of Physicians and Surgeons, New York, where his knowledge of botany turned him first to pharmacology. After an internship at St. Mary's Hospital, Brooklyn, and a service as junior pathologist in the Methodist Episcopal Hospital, he spent a year abroad, more in sight-seeing than in study. In 1890 the "Brooklyn Eagle Almanac" published his first written article, "A List of Plants in Prospect Park." His interest in botany persisted in his early teaching of pharmacognosy and pharmacology at the College of Pharmacy and, later, at College of Physicians and Surgeons. He continued to write on these subjects up to 1904.

Jelliffe was never able to say what it was that led him into neurology and psychiatry. He started in general medical practice in New York,

doing part time work as sanitary inspector for the board of health, but he used to spend his summers working in hospitals. The summer of 1896 was undoubtedly the turning point of his career. That summer he went to the Binghamton State Hospital in his search for what he wanted to do. There he met the man who was to help him shape his life and start him on the work that was to be the main field of his future. Dr. William Alanson White was on the staff at Binghamton; there began the close friendship that was to last and grow until White's death, in 1937. They were of the same stuff, that pair: They thought alike; they worked alike; they played alike. Their intimacy was great, and each supplemented the other in all that he did. They formed an editorial team that had no equal in American medicine.

There is little doubt that it was White who led Jelliffe toward psychiatry, but it was characteristic of the man that he should have turned first to neurology. His botanical training forced him to learn fundamentals first, and fundamentals for him meant morphology; and it was but natural that he should seek first to learn neuroanatomy. Neuroanatomy became a hobby, and for long after he had turned completely to psychiatry and psychoanalysis, neuroanatomy remained a pastime for him.

The summer of 1897 saw Jelliffe at Bloomingdale Hospital and 1898 at Craig Colony. One year before his first neurologic publication, "Preliminary Note on the Cytology of the Brains of Some Amphibia; I. Necturus," appeared in the *Journal of Comparative Neurology.* From then on, pharmacology and botany quickly disappeared from his bibliography, to be gone completely by 1904. His first psychiatric writing was his translation, with White, of Dubois' "The Psychic Treatment of Nervous Disorders," in 1905. By 1913 psychoanalysis begins to creep into his bibliography, to take an even more important place from then on. In that year he and White started the *Psychoanalytic Review.* Up to 1939, when his health began to fail, his articles and books totaled 411 publications.

Jelliffe early entered the field of medical editing because he liked to write and wanted to increase his income. In 1900 he became editor of the *New York Medical News,* and in 1905, associate editor of the *New York Medical Journal.* His first appearance with the *Journal of Nervous and Mental Disease* was in 1902, when he started on his long service as managing editor, which lasted until his retirement, in 1944. In 1907 he and White started the "Nervous and Mental Disease Monograph" series, which has contributed so much to the furtherance of knowledge in this subject. In 1915 Jelliffe and White first published their now standard textbook, "Diseases of the Nervous System."

The *Journal of Nervous and Mental Disease* was Jelliffe's first love, and he clung to it longer than to any other. It was through this journal that he wielded his greatest influence. While many may have skipped hurriedly through the original articles, nobody missed a word of Jelliffe's book reviews. He did practically all of them himself, and there always were many, in an easy-flowing style that offered a fine judgment on the books he read. He spared no punches, and he spared no praise in the straightforward honesty of his criticisms. His enthusiastic advocacy of psychoanalysis, at a time when psychoanalysis had not yet been accorded the recognition it enjoys today, was motivated by that same intellectual honesty that was a basic part of his personality. Even in his later years, when he was too ill to work, his enthusiastic partisanship for what he believed to be true never flagged, as all of us who received his frequent letters well know.

Dr. Jelliffe belonged to many medical societies and held office in most of them. He served as president of the New York Neurological Society, the American Neurological Association, the New York Psychiatric Society, the American Psychopathological Society and the American Psychoanalytic Society. Dr. Jelliffe married Helena D. Leeming in 1894, and they had 5 children, of whom 4 survive. In 1917 he married Bee Dobson, who also survives.

Jelliffe was primarily a physician, an editor and a teacher. Those who worked with him have many pleasant memories of his friendship, his loyalty, his intellectual honesty and his fine, kindly sense of humor. At Jelliffe's jubilee celebration, in 1939, Dr. Adolf Meyer paid him this tribute in his own words: "He lives for all his worth and enjoys it with us."

L. CASAMAJOR, M.D.

# OTTO SITTIG, M.U.Dr.

1886-1944 (?)

According to the "Information Bulletin of the Embassy of U.S.S.R." (May 1945), Otto Sittig, M.U.Dr., professor extraordinarius of neurology and psychiatry in Prague, was murdered by the Nazis in the Oswiecim camp.

Otto Sittig was born in 1886 in Prague, where he graduated in 1911. He was first associated with Prof. Alfred Přibram and later with Prof. Arnold Pick, whose work on aphasia was faithfully carried on by Sittig. Sittig was an excellent clinician, gifted with the greatest patience and critical judgment. Numerous publications on diseases of the central and the peripheral nervous system will remain as his contribution to the advance of neuropathology. He had an unusually fine knowledge of the neurologic literature and tried to do his share in establishing international relations by translating the writings of English authors, among others the work of Hughlings Jackson, into the German language.

Rudolf Altschul.

# Abstracts from Current Literature

## Anatomy and Embryology

THE COURSE OF THE STRIAE MEDULLARES IN THE HUMAN BRAIN. THOMAS H. ALPHIN and WILLIAM T. BARNES, J. Comp. Neurol. **80**:65 (Feb.) 1944.

Alphin and Barnes studied the course of the striae medullares in the brain of an adult white man. The brain had been sectioned serially at 40 microns and stained by the Weil method for myelin. Owing to a somewhat unusual plane of section, which nearly paralleled the course of the striae medullares, it was possible to trace the course of the fiber bundles for a considerable distance. The striae medullares formed a prominent bundle of myelinated fibers on the floor of the fourth ventricle. When traced laterad, the bundle separated into three groups of fibers. The most rostral group, consisting of a small number of fibers, passed directly into the white matter of the cerebellum, which formed the lateral wall of the fourth ventricle at that point. More caudad a few fibers passed into the peduncle of the flocculus. Still farther caudad the majority of the fibers passed ventrad and entered the pontobulbar body external to the restiform body. When the striae medullares were traced medially, they were seen to dip into the medial raphe and, after a complete or partial decussation, to continue ventrally into the region of the arcuate nuclei. They could not be traced farther because of intermingling with ventral external arcuate fibers. Alphin and Barnes suggest that if the external arcuate nuclei be considered as caudally displaced pontile nuclei, the striae medullares would be analogous to the transverse pontile fibers. There is no evidence, however, as to which direction the fibers take. The authors emphasize that the fibers of the striae medullares are not auditory in function.

ADDISON, Philadelphia.

AN EXPERIMENTAL INVESTIGATION OF THE CONNECTIONS BETWEEN THE CORPUS STRIATUM AND SUBSTANTIA NIGRA IN THE CAT. HAROLD ROSEGAY, J. Comp. Neurol. **80**:293 (June) 1944.

Rosegay studied the reciprocal relations of the corpus striatum and the substantia nigra in the brains of 16 cats after experimental injuries. In 6 brains the substantia nigra was destroyed, and in 8 the head of the caudate nucleus was removed or damaged. The animals were allowed to survive for about two weeks after operation. The brains with lesions of the substantia nigra were prepared by the Marchi method for staining degenerating myelin. From the brains with lesions in the caudate nucleus selected sections were stained with cresyl violet to show retrograde cell changes. In addition, 2 brains were used for comparison, 1 from an animal subjected to frontal lobectomy and the other from an animal with a chronic lesion of the substantia nigra. Short protocols are given of the 14 main experiments. Rosegay found that lesions of the head of the caudate nucleus and of the anterior limb of the internal capsule gave rise to retrograde chromatolysis of the pars reticulata and the pars compacta of the substantia nigra. His experiments do not support the idea that the pallidum is a more important terminus than the striatum for efferent fibers from the substantia nigra. The present study suggests that the principal efferent connection of the substantia nigra is with the neostriatum. Thus, in addition to the strionigral and the pallidonigral connections, there are important connections in the reverse direction, viz., the nigrostriatal and the nigropallidal.

ADDISON, Philadelphia.

PHYSIOLOGIC EFFECTS OF BILATERAL SIMULTANEOUS FRONTAL LESIONS IN THE PRIMATE. FRED A. METTLER, J. Comp. Neurol. **81**:105 (Oct.) 1944.

Mettler observed the effects on 12 monkeys of making bilateral simultaneous lesions of varying extent on the frontal lobes and subsequently studied the exact extent of the lesions and their histologic consequences. He had previously studied the effects of unilateral lesions on the hemisphere, and in the present investigation he found that simultaneous removal of subareas of the frontal cerebral cortex may produce a result which is not only quantitatively but qualitatively different from the effect of unilateral operation on the same area. Also, the effects of operations done on the two hemispheres on the same day may be different from the effects produced by allowing an interval of time to elapse between the operations on the two sides. Bilateral simultaneous removal of area 4 immediately produces marked stiffness and resistance to passive movement, and these effects are essentially related to the ablation of that part of area 4 variously known as the suppressor area, the strip region or area 4 S. There is an immediate loss of adult locomotion and manual feeding patterns, and the animal is unable to chew and can only suck its food. Fine digital movements are acutely abolished and chronically impaired. The plantar response becomes difficult to elicit, and the threshold of the patellar reflex is raised. Section of the dorsal columns only slightly ameliorates the resistance produced by removal of area 4 and still further degrades the quality of the motor performance. Another effect noted was that the animals bilaterally deprived of area 4 cortex become abnormally sensitive to the effects of section of the vestibular nerve. Unilateral section of the vestibular nerve in such animals induces a reaction reminiscent of what is seen in carnivora, viz., rolling and fixation of posture.

ADDISON, Philadelphia.

THE DISTRIBUTION OF MYELINATED AFFERENT FIBERS IN THE BRANCHES OF THE CAT'S FACIAL NERVE. S. R. BRUESCH, J. Comp. Neurol. **81**:169 (Oct.) 1944.

To determine the number of myelinated fibers having origin in the geniculate ganglion, Bruesch transected the left seventh nerve 5 to 10 mm. distal to the stylomastoid foramen, just before it divides into its branches to the mimetic musculature. After a lapse of twelve to fourteen days the geniculate ganglia of both sides were removed and serial sections stained with thionine. Counts were made of the total number of cells and of the cells showing chromatolysis. On the right, intact, side, 4.2 per cent of the cells showed some degree of chromatolysis and on the side of operation, 12.4 per cent were so affected. The difference of 8.2 per cent is considered due to the transection. The total average count of cells in the geniculate ganglion was 1,711, and

8.2 per cent of this is 140, the average number showing chromatolysis. The inference is that there are 140 afferent fibers of geniculate ganglion origin in the motor nerves to the mimetic muscles. By gold chloride methods for nerve endings, Bruesch sought the receptors in the muscles connected with these afferent nerves. The only sensory nerve endings appeared to be free terminations in the adventitia of blood vessels in the muscles. Bruesch is inclined to regard these endings as connected with pain fibers. Also, fiber degeneration experiments were made to see how many afferent fibers from the mimetic muscles were tributary to the auricular nerve of the vagus. The facial nerve trunk was severed proximal to the union of the auricular nerve with the facial trunk. The number of myelinated nerves persisting in the peripheral facial nerve trunk twenty-one to thirty-six days after operation averaged 93. There are thus afferent fibers of both facial nerve and vagus nerve origin in the muscular branches of the facial muscles. As no proprioceptors were discovered in the muscles, these fibers are probably pain fibers. Bruesch considers this anatomic evidence to support the clinical views as to the existence of neuralgias of both geniculate ganglion and vagus nerve origin.

ADDISON, Philadelphia.

STUDIES ON THE NEUROMOTOR SYSTEMS OF STYLONYCHIA PUSTULATA AND STYLONYCHIA MYTILUS. YUEH-TSENG CHEN, J. Morphol. **75**:335 (Nov.) 1944.

Both the hypotrichous ciliates (Stylonychia pustulata and Stylonychia mytilus) possess a neuromotor apparatus. The neuromotor systems of these two species are similar. Each system consists of membranelles and their associated fibrils, undulating membrane and its basal fibril, dorsal cystostomal fibrils, ventral cystostomal fibrils, postesophageal fibrils, and anal, caudal and marginal cirri. The frontal cirri and the ventral cirri do not appear to be connected with the neuromotor system.

In S. pustulata, the five anal cirri are each supplied with a longitudinal fibril, while, in addition, one to three anal cirri each, has a transverse fibril. In S. mytilus, each of the five anal cirri is supplied with a bundle of five to eight longitudinal fibrils, but no transverse fibrils have been found. Each of the three caudal cirri is supplied with a single fibril in S. pustulata, and with a bundle of fibrils in S. mytilus. A single fibril connects the marginal cirri near the base. Each marginal cirrus has a terminal fibril running inward toward the central part of the body.

A deeply stained (hematoxylin) mass near the posterior end of the adoral band of membranelles in S. pustulata may be the neuromotorium. The silver impregnation technic did not reveal any silver line system.

REID, Boston.

## Physiology and Biochemistry

EFFECT OF ANOXIA ON THE VESTIBULAR APPARATUS. A. POPOV and I. BORSHCHEVSKI, Am. Rev. Soviet Med. **1**:310 (April) 1944.

Popov and Borshchevski studied the effect of hypoxemia on 31 persons who were subjected to rocking on a four pole swing or placed in a low pressure chamber. Sixty-two experiments were performed on subjects while rocking in the swing under normal breathing conditions and while breathing a mixture with a lowered content of oxygen (8 to 12 per cent). The breathing mixtures were inhaled through a special mask. The rarefied mixture was inspired as the subject was moved in the Bárány chair and then subjected to the oxygen respiration test. He was then transferred to the four pole swing for fifteen minutes' rocking. This was followed by the oxygen respiration test after which the mask was removed, and normal respiration ensued. The data show that in some persons pallor, vertigo, blackout, sweating, cyanosis, nausea and vomiting were more pronounced under conditions of rocking and hypoxemia.

Two other series of experiments were undertaken in an effort to study the effect of altered barometric pressure on nystagmus. The results were uninformative, and the authors concluded that more sensitive methods of investigation must be devised.

GUTTMAN, Philadelphia.

PYRIDOXINE DEFICIENCY IN SWINE, WITH PARTICULAR REFERENCE TO ANEMIA, EPILEPTIFORM CONVULSIONS AND FATTY LIVER. MAXWELL M. WINTROBE, RICHARD H. FOLLIS JR., MITCHELL H. MILLER, HAROLD J. STEIN, RAUL ALCAYAGA, STEWART HUMPHREYS, ADOLPH SUKSTA and GEORGE E. CARTWRIGHT, Bull. Johns Hopkins Hosp. **72**:1 (Jan.) 1943.

Pigs, about 3 weeks old, were fed only crystalline vitamins, in addition to a basal diet. Microcytic anemia developed in from three to fifteen weeks in all the animals which received all the crystalline vitamins but pyridoxine hydrochloride. It was noted that the anemia which developed in pigs not given calcium pantothenate or choline chloride, in addition to the deprivation of pyridoxine hydrochloride, was similar in all respects to that observed in pigs lacking only the pyridoxine. A sharp increase in the reticulocyte count followed the administration of pyridoxine hydrochloride. These reached a peak on the second to the sixth day after administration of the first dose of pyridoxine. The increase affected particularly the hemoglobin and the volume of packed red cells, as well as the size of the corpuscles. The highest increase in the reticulocyte count, in the hemoglobin concentration and in the volume of packed red cells was observed when the anemia was most pronounced and large amounts of pyridoxine hydrochloride were given intravenously. Pronounced and uniform changes were observed in the spleen, liver and bone marrow of the animals in which pyridoxine anemia developed. The changes related to the presence of anemia were hemosiderosis in the spleen, liver and bone marrow and hyperplasia of the bone marrow. Mobilization of iron from the tissues and its utilization in blood formation are indicated by the disappearance of hemosiderosis and a fall in the iron content of serum following treatment with pyridoxine. Pathologic changes in the liver consisted of fatty infiltration and could be seen as vacuoles in the cells of the central portions of the hepatic lobules. The observations indicate that fatty infiltration of the liver occurs when either pyridoxine or choline or both are not furnished as supplements to the diet. Convulsions were observed in 20 of 26 pigs not given a supplement of pyridoxine hydrochloride, as well as in 6 of 16 pigs fed fractions of liver poor in pyridoxine. There was no consistent relationship between the time of onset of convulsions and the time at which significant anemia appeared. The convulsions ceased promptly after the administration of pyridoxine hydrochloride in the doses used in the treatment of the anemia. No changes in the brain were noted in any of the pyridoxine-deficient animals except in the lower portion of the medulla,

where fibers in the ascending sensory tract had lost their myelin sheaths. The changes were interpretated as being part of the degeneration of sensory neurons resulting from pyridoxine deficiency. The nature of the mechanism by which pyridoxine deficiency arrests the synthesis of hemoglobin and elevates the iron content of the serum is not understood.

PRICE, Philadelphia.

DETERMINATION OF CARBONIC ANHYDRASE IN HUMAN AUTOPSY TISSUE. W. ASHBY and D. V. CHAN, J. Biol. Chem. **151**:515, 1943.

In 1932 Meldrum and Roughton isolated from mammalian red blood cells a highly active enzyme which they called carbonic anhydrase. This enzyme catalyzes the reaction $H_2CO_3 \rightleftarrows CO_2 + H_2O$ and is responsible for the accelerated excretion of carbon dioxide from the blood. In any assay of the enzyme in tissues the presence of blood has presented difficulties. In this report a new adaptation of a method for measuring the blood content of tissues is described. The reproducibility of the technic is illustrated by complete determinations on adjacent portions of the central nervous tissue which indicate an average difference of 5 per cent.

PAGE, Cleveland.

OXIDATION OF FRUCTOSE BY BRAIN IN VITRO. J. R. KLEIN, J. Biol. Chem. **153**:295, 1944.

Fructose does not maintain the electrical activity of the cerebral cortex in the hepatectomized animal. However, whole brain and cortex oxidize fructose in vitro. These facts may be explained by assuming that the brain cells are impermeable to fructose in vivo or that the oxidation of fructose is not concerned in the maintenance of cortical activity. The latter supposition makes it necessary to assume that the metabolism of fructose by brain differs from the metabolism of dextrose, since the latter does support cortical activity in the hepatectomized animal. In the present work, the oxidation of fructose by brain preparations was studied in vitro. The data obtained indicate that the oxidation of fructose by brain in vitro follows the same pattern as the oxidation of dextrose. Thus, the data support the hypothesis that brain cells are impermeable to fructose in vivo.

PAGE, Cleveland.

WATER, NITROGEN, AND ELECTROLYTE CONCENTRATION IN BRAIN. L. EICHELBERGER and R. B. RICHTER, J. Biol. Chem. **154**:21, 1944.

Procedures are described by Eichelberger and Richter for water and electrolyte analyses of the cerebral hemispheres and the cerebellum. Total water, nitrogen and electrolyte concentrations were determined in brain, which was removed by bilateral craniotomy from normal dogs. For analyses the brain was separated into the cerebral hemispheres and the cerebellum with the brain stem. Analyses of the right and left hemispheres from the same animal gave the same values. The mean average results for the hemispheres expressed as units per kilogram of hemisphere, are as follows: total water 761.3 Gm., $\sigma \pm 8.3$; chloride 36.71 millimols, $\sigma \pm 1.05$; sodium 51.0 millimols, $\sigma \pm 2.4$; potassium 95.6 millimols, $\sigma \pm 4.7$; calcium 1.07 millimols, $\sigma \pm 0.07$; magnesium 5.63 millimols, $\sigma \pm 0.56$, and total nitrogen 18.9 Gm., $\sigma \pm 0.3$. The cerebellum with the brain stem gave the following mean average results: total water 745.0 Gm., $\sigma \pm 7.0$; chloride 35.19 millimols, $\sigma \pm 0.89$; sodium 50.8 millimols, $\sigma \pm 1.7$; potassium 92.7 millimols, $\sigma \pm 4.0$; calcium 1.07 millimols, $\sigma \pm 0.07$; magnesium 5.40 millimols, $\sigma \pm 0.30$, and total nitrogen 19.1 Gm., $\sigma \pm 0.5$. Because the analyses of the hemispheres and the cerebellum following extraction of the dried tissue with ether and petroleum ether gave low concentrations of chloride, sodium and potassium, the analytic results were not expressed in terms of fat-free tissue. The analytic results are of value for further experimental work on brain as control data, since it is impractical to take control brain tissue from the experimental animal.

PAGE, Cleveland.

PIAL CIRCULATION AND SPREADING DEPRESSION OF ACTIVITY IN THE CEREBRAL CORTEX. A. A. P. LEAO, J. Neurophysiol. **7**:391 (Nov.) 1944.

Leao observed the pial vessels of rabbits under dial anesthesia by means of a compound microscope and studied the variations in their caliber before, during and after the appearance of depression of the electrical activity resulting from electrical stimulation of the cortex. He observed a wave of marked dilatation of the pial vessels and increased blood flow traveling over the cerebral hemisphere concomitantly with the wave of depression in the electrical activity. Arteries increased in size from 50 to 100 per cent, and the veins became as scarlet as the arteries. The presence or absence of convulsive activity had no correlative variation with the degree of vascular change. Leao concluded that the vascular response was secondary to a local change in the activity of the nerve elements and that the increase in blood flow probably influenced in turn the activity of the cortical neurons.

FORSTER, Philadelphia.

MIDBRAIN AUDITORY MECHANISMS IN CATS. H. W. ADES, J. Neurophysiol. **7**:415 (Nov.) 1944.

Ades recorded from a cathode ray oscillograph the responses to sound stimuli from various parts of the midbrain of the cat. He found that the contribution of discharge through the inferior collicular commissure was negligible in the total activity of the inferior colliculus. The contribution of the contralateral ear to collicular response was found to be slightly greater than that of the homolateral ear. The functional bilateral equality in auditory conduction from the ears is probably due to bilateral terminations of secondary auditory fibers in the superior olivary nucleus. Significant numbers of fibers from the lateral lemniscus by-pass without synapsing in the inferior colliculus. The inferior colliculus was found to discharge through the superior colliculus, and it is considered an important reflex center for auditory integration.

FORSTER, Philadelphia.

RECOVERY OF FIBRE NUMBERS AND DIAMETERS IN THE REGENERATION OF PERIPHERAL NERVES. E. GUTMANN and F. K. SANDERS, J. Physiol. **101**:489, 1943.

Gutmann and Sanders studied the effect of crushing, cutting, suturing and nerve grafting on the number and size of the nerve fibers in the peripheral and the central stumps of the severed nerves and in the various nerve grafts. After the nerve was crushed or cut, the central stump regularly exhibited a decrease in size of all its constituent fibers, an observation suggesting that the outgrowth from the central stump is really an outflow of protoplasm from the neurons.

After the crushing, the peripheral stump was completely reconstituted with respect to both the number

and the size of fibers within two hundred and fifty to three hundred days. After the suturing or grafting, the peripheral stump of the regenerating nerve showed a deficit in number and in average size of the fibers even three hundred and sixty-four days after operation. No such nerve was observed ever to recover fully with respect to number or to size of fibers. There was a deficit particularly in the number of large fibers. The deficit in number of fibers in the peripheral stump was particularly noticeable below alcohol-fixed grafts, in which the number attained was only 60 per cent of the number present in the central stump. In such instances recovery of function was incomplete.

THOMAS, Philadelphia.

EXPERIMENTAL EDEMA OF THE BRAIN: IV. CEREBRAL CIRCULATION. S. OBRADOR ALCALDE and J. PI-SUÑER, Bol. d. Lab. de estud. med. y biol. **1**:99 (June) 1942.

The difference in oxygen content between arterial and venous blood was studied in adult dogs in which experimental edema of the brain had been produced by lesions in the region of the fourth ventricle. Simultaneous specimens of blood were taken from the femoral artery and the external jugular vein ten and fifteen to twenty minutes after the lesions were made in the fourth ventricle. The cerebral circulation was studied in this way in 8 animals. In 5 of them there was no significant change in the difference in oxygen content between venous and arterial blood. In 3 dogs there was a diminution of this difference, indicating a sudden increase in blood flow. Although the data are not conclusive, the authors indicate that in some cases an increase in circulation may be a factor in accounting for the appearance of edema of the brain.

SAVITSKY, New York.

## Psychiatry and Psychopathology

CONVULSIVE SHOCK THERAPY IN INVOLUTIONAL STATES AFTER COMPLETE FAILURE WITH PREVIOUS ESTROGENIC TREATMENT. A. E. BENNETT and C. B. WILBUR, Am. J. M. Sc. **208**:170 (Aug.) 1944.

Bennett and Wilbur reviewed the records of 500 cases of psychoses and psychoneuroses occurring in women between the ages of 31 and 65 years. Seventy-five of the patients had received estrogens as therapy for the mental disorder. The condition of 41 was classified as involutional melancholia. Of the 75 patients, 64 received some form of shock therapy, but for 11 psychotherapy alone sufficed. A course of from six to eight shock treatments was given over a period of two to three weeks. After active shock treatment, patients remained in the hospital from ten days to two weeks for reeducative psychotherapy. The authors concluded that estrogens were of no value in the treatment of psychiatric disorders except for symptomatic relief of vasomotor symptoms.

MICHAELS, M. C., A. U. S.

RESPONSES OF SCHIZOPHRENIC PATIENTS TO INDUCED ANOXIA. W. CORWIN and S. M. HORVATH, J. Nerv. & Ment. Dis. **99**:149 (Feb.) 1944.

The impetus to studies of the effects on the human organism of exposure to environments containing low percentages of oxygen has come both from the field of high altitude aviation and from the various shock therapies of psychoses. To study these effects, Corwin and Horvath subjected 10 male schizophrenic patients to atmospheres containing, respectively, 14.6, 5.2 and 4.2 per cent of oxygen. The neurologic manifestations of anoxia were in general similar to those attributed by Levine and Schilder to inhalation of nitrogen, with the production of four phases—a stage of restless movement, a myoclonic stage, a rhythmic stage and a tonic stage. Various changes in behavior occurred. No notable improvement was seen in any of the patients; on the other hand, no untoward permanent mental or physical changes were demonstrated, even with exposure to the 4.2 per cent oxygen mixture which corresponds to an altitude of approximately 31,000 feet (9,500 meters).

CHODOFF, Langley Field, Va.

NEUROTIC MANIFESTATIONS OF THE VOICE. MORRIS BRODY, Psychoanalyt. Quart. **12**:371, 1943.

Brody points out that the voice is a sensitive reflector of emotional states and is used by the ego as a vector for neurotic symptoms and defense mechanisms. To hear the voice solely for what it has to say and to overlook the voice itself deprives the analyst of an important avenue to emotional conflicts. The defensive operations of the ego are the tools with which the analyst must work; and since resistances are constantly being acted out by means of the voice, it is doubly important that such behavior be exposed and analyzed. Interpretations regarding changes in voice are usually effective because they are readily appreciated by the patient. The most difficult voices to recognize as pathologic are those arising from vigorous defensive processes in the past which have developed into permanent character traits.

PEARSON, Philadelphia.

SOME ASPECTS OF A COMPULSION NEUROSIS IN A CHANGING CIVILIZATION. HENRY LOWENFELD, Psychoanalyt. Quart. **13**:1, 1944.

There has been considerable discussion in psychoanalytic circles about the interrelationship of the problems of psychoanalysis and those of culture. There is a difference between the content of the neuroses of the present day and those described by Freud. The neuroses occurring in different epochs present very different symptomatic pictures and offer different preventive and self-curative possibilities. Freud expressed the opinion that the neurosis is a product of the great demands of civilization on man's instincts. Civilization, however, offers ever changing aids for the mechanisms of defense and channels for sublimation. Perhaps cultural development is actually motivated by man's endless need for help in his struggle with his instincts. In the well balanced society depicted by Freud in his earlier writings the main task of analysis was to bring neurotic conflicts into consciousness. If the patient recognized that his anxieties and their projection into the world were based on childhood distortions of reality, he would find his normal place in a balanced world. The lifting of repressions was the decisive factor, because the ideals of civilization supported the ego in its struggles with the instincts. Today this secure social basis has vanished. Social reality, instead of being a standard for the correction of the fantasies of the unconscious, is now a constant provocation for these fantasies. The chaotic condition of society and the tensions expressed in the battles of nations are like a mighty breaking forth of instincts from their civilized domesticated and sublimated forms. Adults, in their attitudes toward nature, the cosmos and society, were protected formerly against a feeling of childhood helplessness by trust in God, by pantheistic

experiences and by belief in scientific progress. In a society in which institutions and their meaning are changing, homosexual sublimations tend to break down, because homosexuality in its sublimated form plays an important role in social relations and in the structure of society.

When reality becomes a provocation to the unconscious, its role in overcoming anxiety is altered, because the ego is compelled to ward off external situations which provoke forbidden unconscious wishes. Social theories which were originally developed for the purpose of understanding and mastering reality now replace cognition and take over the function of warding off the threat and provocation of reality; they become defense mechanisms. When these theories threaten to lose their protective character, they must by compulsion be maintained, so that the end result is no longer a cognition, but, rather, a repudiation, of reality. Different epochs offer a man various methods of overcoming the problems arising from his biologic instincts. He seems to need certain general concepts to make it possible for him to keep his equilibrium in the difficult situations between danger and instinct. These concepts contain his childhood problems and offer solutions for them. In epochs of cultural stability the tensions reach a balance, and the person lives out his childhood conflict in later life in a more objective way. As long as the adult struggled above all with the unknown and the dangerous in nature and the cosmos, the religious concept proved a satisfying solution. When these solutions, or their derivations, lost their force, the solution of conflicts in a sublimated form became more difficult, and man was driven to instinctual outbreaks, neurotic reactions and specific defense mechanisms. The struggle with man-made civilization led to the formation of theories and ideologies which have the same functions as religious concepts but can fulfil these functions only insufficiently because they are constantly endangered by reality. The functional background of such ideologies is difficult to penetrate because they represent a normal attempt at a solution, because at the present stage of civilization they seem to be rational and because analysts themselves participate in such ideologies.

PEARSON, Philadelphia.

GASTRODUODENAL DISORDERS. WILLIAM H. DUNN, War Med. **2**:967 (Nov.) 1942.

Dunn reviews the literature, particularly the British, on gastroduodenal disorders in military patients. These constitute the most important medical problem of the war and the most prevalent disease in soldiers. In over 50 per cent of cases the disturbance is said to be due to peptic ulcer.

The frequency of gastroduodenal disorders appears to be related to the inadequate screening of the recruits with a history of ulcer or with a pronounced neurotic personality structure. One may anticipate that patients with such a disorder will be one of two types: (1) men with driving ambitions and a high sense of responsibility, who have a strong desire to enter the service but who are inclined to worry about their home responsibilities, and (2) men with a somewhat hysterical personality structure who are strongly attached to their families and are often characterized as "mama's boy."

A contributory factor to the development of gastroduodenal disorder is the prolonged state of tension which arises in men mobilized for war and exposed to hostile action, with little opportunity to strike back.

PEARSON, Philadelphia

TROPICAL NEUROPSYCHIATRY. JAMES L. MCCARTNEY, War Med. **3**:351 (April) 1943.

Fifty per cent of tropical diseases are parasitic in origin and therefore are not likely to be transplanted to the United States because the climate here is unfavorable to the parasite hosts. The other 50 per cent are known to have neurologic sequelae, and it was recognized in times past that residence in the tropics often had a permanent effect on the personality. Thirty-six per cent of American missionaries were furloughed home because of neuropsychiatric problems, and the various nations who maintained armed forces or business offices in the tropics have insisted on only a short tour of duty in tropical climates for their employees and soldiers.

There is a strong probability, therefore, that many members of the American armed forces will be invalided from tropical duty because of neuropsychiatric effects of their tropical residence. They will show the effects of some of the following conditions:

1. Residence in the tropics sooner or later causes a reduction in blood pressure and in the basal metabolic rate, as a result of the excessive heat and the light of the sun.

2. The excessive light of the sun may result in the development of night blindness.

3. Neurasthenia is common in the tropics. Some authors believe it is the result of the excessive sunlight because it is worse among blondes, but undoubtedly it is due also to the different milieu. In the tropics moral standards are lower; human values are not worth mentioning, and intemperances of every kind are the order of the day. Sexual promiscuity is to be found everywhere, and as a result psychic conflicts and guilt feelings are set up in the white man's conscience, particularly as at first the sexual system is stimulated by the climatic conditions. The neurasthenic person attempts to overcome his unpleasant feelings by overindulgence in stimulants. The white man in the tropics has a great danger of becoming neurasthenic and, secondarily, of becoming chronically addicted to alcohol.

4. The effects of alcohol are more severe in the tropics. Korsakoff's syndrome and delirium tremens are more frequent there than in temperate climates.

5. The use of alcoholic beverages, with the natural limitation of diet which it causes and which results also from the fear of intestinal infection, frequently leads to vitamin deficiencies. Vitamins A, C and B are those most deficient in the tropics, lack of vitamin B causing beriberi, pellagra, anemia and multiple neuritis.

6. Dietary intoxications, such as lathyrism, and food poisoning, cysticercosis and dysenteries, are common. The last-mentioned condition may result in displacement of the libido from the genital to the anal zone.

7. Neurologic sequelae often follow infection with worms and flukes. Trypanosomiasis, malaria, leprosy, relapsing fever and dengue all cause involvement of the central nervous system, with neurologic signs and changes in personality as frequent sequelae.

8. Although syphilis is common, tabes and dementia paralytica are rare.

9. There are many psychic reactions to tropical diseases similar to those in temperate climates and based on the same unconscious conflicts. Many of these sequelae, and many of the diseases themselves, could be prevented by insistence on precautions in personal hygiene and by preparing soldiers and sailors for meeting the moral hazards of tropical life.

PEARSON, Philadelphia.

ETIOLOGIC FACTORS IN THE ADJUSTMENT OF MEN IN THE ARMED FORCES. DAVID LOUIS STEINBERG and MARY PHYLLIS WITTMAN, War Med. **4**:129 (Aug.) 1943.

Steinberg and Wittman report the results of a differential study of sociologic, developmental, personality and adjustment characteristics of 158 men attached to the medical corps. The subjects included 22 patients, chiefly psychoneurotic, in a psychiatric unit and 87 patients, largely psychotic, who had been discharged from the Army within the past year and a half and were now in the veterans' unit of a state hospital.

A battery of tests, including the Elgin developmental history, the Guilford personality scale and the Bell adjustment inventory, was used.

The personnel of the medical corps unit and the patients in the psychiatric unit had an educational level approximately that of graduation from high school, while that of the patients in the state hospital was lower. The length of military service was longer in the control groups than in the two groups of patients studied. Subjects in civilian life held two or three times as many positions as did the subjects in the control groups. Moderate drinking was most frequent in the control groups, while total abstinence and infrequent drinking occurred more often among the patients. There was a relatively higher number of divorced persons among the patients than among the control groups. The patients tended to love their mothers rather than their fathers, to have emotionally unstable mothers and to have mothers who were oversolicitous as compared with the mothers of the control group. The psychotic patients had a history of poorer adjustment during their early home life and school life than did the psychoneurotic patients or those of the control group. The psychoneurotic patients had a history of poorer adult health, social and emotional adjustment than did either the psychotic patients or the control group.

On the Guilford scale, the psychoneurotic and the psychotic patients showed a greater tendency to social introversion, depression and cyclothymia, and the control groups, a greater tendency to thinking introversion and to a care-free disposition.

The Bell scale for adults indicates levels of adjustment in five fields: health, home, social problems, emotion and occupation. On this scale the psychoneurotic group showed significantly more maladjustment in their social life than did the group of medical corps personnel.

Self evaluation of poor social and emotional adjustments in adult life characterized the psychoneurotic group, while maladjustment in the sexual and social life characterized the psychotic group.

The authors' studies indicate that a person who is characterized by strong cyclothymic reactions and traits of social introversion and depression, i. e., the person who is shy and self conscious, withdraws from social contacts and has strong emotional reactions with feelings of depression, unworthiness and guilt and tendencies to fluctuations in mood, flightiness and instability, makes a poor soldier, particularly if he has shown these symptoms before induction. The authors found an overlapping of specific etiologic factors between the psychoneurotic, psychotic and control groups, but they point out that the level of adjustment is not due to the presence or absence of any specific factor but is the result of the number and intensity of the factors.

They believe that rating forms, such as they have used, could be developed and standardized for use at classification centers and in camps to determine the status of borderline persons who are not well adjusted but are not such unquestionably poor psychologic risks as to be rejected by the induction boards. Such tests would be useful also in helping the examining psychiatrist at the induction center in his evaluation of the inductee, as it would give comparable results at various centers. If used routinely, the results of such studies would be of importance for future research.

PEARSON, Philadelphia.

REACTIVE ANXIETY AND ITS TREATMENT. G. GARMANY, Lancet **1**:7 (Jan. 1) 1944.

Garmany discusses cases of reactive anxiety in a British naval depot. The treatment is chiefly outpatient in type, patients continuing in their normal work routine. This, the author believes, is the best occupational therapy. Of 1,342 patients with this type of neurosis, 1,171, or 87.7 per cent, were returned to active duty in three months.

The author stresses the importance of distinguishing between those who are consciously, and often brazenly, avoiding duty and those who are suffering from an accumulation of greater than normal fear. The first group "never develop reactive anxiety because they never permit a conflict to develop at all. The problem they present is not a medical one and they should find no sanctuary with the psychiatrist." All treatment is based on honesty with the qualification that "there are a few occasions where an economy of truth, not inconsistent with the policy of honesty, is better therapy. With some men a degree of self-deception and permitted repression may be less wounding to the ego, and achieve a cure more quickly, than perfect clarity of insight rigorously demanded. Unjustified self-esteem may be of great assistance in rehabilitation, and should not be attacked indiscriminately."

As a first step in treatment, it should be made clear that the responsibility for cure lies with the patient. The physician helps him to get back his confidence. An ideal complete cure must not be assumed. The reality of symptoms must not be questioned by the physician, but he must impress the patient with the realization that they are not incapacitating. The quantitative difference between his present fear reaction and that which he had experienced before must also be made clear, for the author believes that the "reactive anxiety of war should be regarded as a condition pathological not in its nature but in its maintenance and continuity." From then on, treatment consists in steering carefully between too much condonement (so deteriorating to good group sense) and antagonizing disparagement. Symptomatic treatment must be vigorously employed and in nearly all cases an involved analytic approach avoided.

MCCARTER, Philadelphia.

## Diseases of the Brain

UNUSUAL FORMS OF NYSTAGMUS. HENRY C. SMITH and F. REGIS RIESENMAN, Arch. Ophth. **33**:13 (Jan.) 1945.

Smith and Riesenman discuss 3 cases of unusual and comparatively rare forms of nystagmus. Two were cases of ocular nystagmus, volitional and occupational, and the third was a case of mixed nystagmus, due to compression of the upper cervical portion of the spinal cord.

Fundamentally nystagmus may be of vestibular, cerebellar, cerebral, upper cervical or ocular origin. The optic system is involved in all forms, but it is only in the ocular type that it is directly affected. In

all other forms it is involved indirectly by way of the vestibular system. The vestibular system may be the seat of origin of irritative phenomena and may transmit the abnormal impulses to the ocular system, or the pathologic change may be in the cerebrum, the cerebellum or the upper cervical portion of the cord, in which event the vestibular system, together with the posterior longitudinal fasciculus, acts as a nucleus for the mediation of the abnormal impulses. The occurrence of nystagmus with lesions of the cord is uncommon, but a review of the literature indicates that a number of cases have been reported. It is assumed that the nystagmus in the authors' case was the result of interference with the spinocerebellar pathways, resulting in abnormal stimulation of the cerebellum, which, in turn, involved the optic system.

SPAETH, Philadelphia.

CAVERNOUS ANGIOMA OF THE MEDULLA. ROQUE GRAZIANO, Rev. argent. de neurol. y psiquiat. 8:415 (Dec.) 1943.

Graziano believes that his is the first case of cavernous angioma in the medulla oblongata reported. A 30 year old Argentinian farmer was admitted to the hospital Jan. 27, 1943 and died the next day. The illness was of six months' duration. It began with hiccups, which lasted two days and recurred two days later, this attack lasting four hours. At that time he complained of sore throat and numbness of the right side of the face and tongue. His family noted that the right palpebral fissure was wider than the left. He then began to complain of intense pain in the back of the head and of headaches and dizziness. In a few days he was unable to walk. He also had difficulty in speaking. He was hospitalized for a month. He then worked for four months in spite of headaches and dizziness; soon afterward he noted numbness of the entire right side of the body and clumsiness of the right hand. Ten days prior to admission he was sleepless and became delirious; for four days he was unable to talk, chew or swallow.

On examination the patient looked acutely ill and was confused. The right palpebral fissure was wider than the left; the jaw deviated to the right; the right pupil was smaller than the left; nystagmus was present with lateral and upward gaze; there was some diplopia; the pupillary reactions were normal and the right corneal reflex was diminished. There was atrophy of the borders of the tongue, with deviation of the tongue to the left. Nasal regurgitation occurred. There were aphonia and marked dysarthria. The response to pinprick was diminished on the left side of the face. Finger to nose ataxia was present on the left side. The knee jerks could not be obtained. There was no Babinski reflex or other confirmatory sign. The gait could not be studied. The clinical diagnosis was syringobulbia.

At autopsy a soft enlargement of the left side of the medulla was seen. A transverse section in the region of the pontobulbar junction showed an oval tumor, 1.5 by 1 cm., which was dark red and definitely delimited. The inner border reached the midline; the ventral border extended to the region of the pyramids and the dorsal to within 2 or 3 mm. of the floor of the fourth ventricle. A more caudal transverse section, at the level of the olives, showed the tumor to be larger and more irregular, extending beyond the midline and laterally to within 2 mm. of the outer border of the medulla. The tumor was apparently composed of many cavities, of various sizes, which were filled with blood. Microscopic examination showed the tumor to be composed of many dilated blood vessels, varying in size; the walls of the vessels were occasionally adherent to each other and sometimes were even torn, so that some of the cavities communicated with each other. Most of the blood vessels were separated by bands of fibrous tissue and the remains of necrobiotic bulbar parenchyma. There was no angioblastic tissue. The diagnosis was a cavernous angioma of the medulla.

SAVITSKY, New York.

## Vegetative and Endocrine Systems

THE SYNDROME OF PRECOCIOUS PUBERTY, FIBROCYSTIC BONE DISEASE AND PIGMENTATION OF THE SKIN: ELEVEN YEARS' OBSERVATION OF A CASE. BERNARD M. SCHOLDER, Ann. Int. Med. 22:105 (Jan.) 1945.

Scholder reports the case of a 19 year old girl who has been under his observation for eleven years. Delivery was attended by considerable trauma to the mother. Vaginal bleeding began suddenly in the child at the age of 3 years and recurred at irregular intervals for the next two years; since the age of 7 it has been a constant feature. Tenderness of the breasts appeared at 3 and the mammae became prominent at 4 years. At the age of 5, pubic hair appeared, and facial asymmetry became apparent. The syndrome of precocious puberty, fibrocystic changes in bone and pigmentation of the skin has been compatible with an otherwise normal life and development. Physical examination revealed slight facial asymmetry, decrease in size of the left limbs and small stature. Growth ceased at the age of 12, with a maximum of 61.5 inches (156 cm.). The results of laboratory studies were not remarkable except for an increase in the amount of "sex hormone" in the urine when the patient was 9 years of age. Roentgenographic studies have shown profound and widespread changes in bone condensation and absorption, but there has been only slight progression of these changes over the past ten years.

Scholder advances the hypothesis that the syndrome results from a hypothalamic (pituitary) parathyroid disturbance.

GUTTMAN, Philadelphia.

# Society Transactions

## ILLINOIS PSYCHIATRIC SOCIETY

DAVID SLIGHT, M.D., *President*

*Regular Meeting, Dec. 7, 1944*

**Experimental Study on Treatment of Dementia Paralytica with Penicillin.** DR. C. A. NEYMANN, Chicago; DR. G. HEILBRUNN, Manteno, Ill., and DR. G. P. YOUMANS, Chicago.

Intravenous and intramuscular injections of penicillin sodium over a period of one to two weeks were ineffective in the treatment of dementia paralytica because the hematoencephalic barrier could not be breached. No trace of penicillin was found in the spinal fluid regardless of whether the drug was administered in massive doses (up to 1,000,000 Oxford units of penicillin intravenously within three hours or 3,100,000 Oxford units intramuscularly over a period of one week) or whether it was given in conjunction with induction of artificial fever or with injections of bile salts.

The intracisternal route was finally chosen, but this method proved dangerous if more than 30,000 Oxford units of penicillin was injected. The daily injection of this dose intracisternally for longer than five consecutive days was also hazardous, causing encephalopathy, with rigidity of the neck, coma and convulsions.

Two of 5 patients treated with penicillin died as the result of the therapy. One patient showed clinical improvement. Examination of the spinal fluid revealed that the chronic pachymeningitis and leptomeningitis of 3 patients were favorably influenced. The syphilitic involvement of the parenchyma in the depths of the cortex, however, probably remained unchanged.

### DISCUSSION

DR. FRANCIS GERTY, Chicago: This report is interesting to one like me who has had no experience in treatment with penicillin. There is no reason to be discouraged as to the results of treatment and clinical improvement on the basis of experience in 5 cases. I well remember the first patients with dementia paralytica whom I treated by induction of malarial fever, using two methods. Only 3 or 4 patients in the series improved, as I recall, and the first 2 died. Of course, I chose the patients with the worst prognosis, as I did not want to take a chance with any other kind. Penicillin therapy must be considered as a chemotherapeutic method, regardless of the origin of the material. Experience with chemotherapy of dementia paralytica has always been somewhat discouraging—the results being similar to those that Dr. Neymann and his associates have reported for penicillin therapy. The enemy has become entrenched in some way and has already caused considerable destruction. An approach by chemical warfare, apparently, does not get through to him. It reminds me of the old fable of the man who would not take off his coat when the cold wind blew hard, but who yielded to the gentle beams of the sun: It seems that fever treatment has been more effective in treating dementia paralytica because it gets at the enemy better than other methods. I should like to ask Dr. Neymann about the rate of recovery of penicillin from the urine after injection by the intraspinal route.

DR. ROBERT GRONNER, Elgin, Ill.: Why not the lumbar route instead of the more heroic cisternal route?

My associates and I have so far treated only 2 patients, and this by the intramuscular route, with a comparatively low dosage of 1,200,000 Oxford units of penicillin extended over a period of nearly one week. In spite of the apparent inability of penicillin to get through the hematoencephalic barrier, we obtained some good clinical results: Both patients showed definite improvement in their general condition and in their ability to enunciate test words which they had been unable to enunciate before treatment. In 1 patient the patellar reflexes returned, after having been absent for many years. I followed up this patient and found that the patellar reflexes had disappeared again, after three weeks, first on one side and then on both sides. I saw the patient only last week, and he was in about the same condition as before the beginning of treatment, which was given last August. He is now suffering from a typical "cord bladder." Altogether, we are under the impression that the therapy produces improvement, but apparently it could not be maintained.

Dr. Neymann and Dr. Heilbrunn are quite right in taking the more heroic attitude and giving large doses of penicillin and using various routes. However, the 2 patients we treated were men who had not deteriorated, both were active in their occupations and were making a living, so that we did not feel justified in using too heroic a method. One patient had had malarial treatment, with little improvement; the other has an aneurysm of the aorta, which precluded fever therapy.

Serologic tests did not reveal anything of importance except flattening of the colloidal gold curve and a slight decrease in the protein content of the spinal fluid. The fluid of 1 patient gave a 1 plus Wassermann reaction after completion of the treatment, after having persistently given a 4 plus reaction.

Further clinical and experimental study will be carried on at the Elgin State Hospital.

DR. F. HILLER, Chicago: Dr. Neymann and his associates emphasized the fact that the hematoencephalic barrier is not overcome by penicillin, since the drug was not found in the spinal fluid after intravenous injection. They based their method of administration of penicillin into the subarachnoid space on this observation. May I point out that the absence of penicillin in the spinal fluid would indicate only the impermeability of the blood–cerebrospinal fluid barrier to penicillin, but not that of the hematoencephalic barrier proper? It is known from experience that the permeability of the endothelium of the choroid plexus may differ from that of the pia-glia membranes and the vessel walls. Since a therapeutic substance injected into the subarachnoid space penetrates only into the superficial layers of the cortex, such a method does not appear to offer the ideal therapeutic approach, in view of the pathologic character of dementia paralytica. The process is a true syphilitic encephalitis, with inflammatory lesions predominantly in the gray substance of the cortex and the basal ganglia. One would think that such lesions could be reached with far better success by way of the blood than of the cerebrospinal fluid. To facilitate penetration into the brain tissue,

a hope which Dr. Neymann also cherishes, one may have to improve certain qualities of the penicillin. High dispersibility of particles and alkalinity of the solution may achieve penetration of the hematoencephalic barrier proper without lowering the threshold of the blood–cerebrospinal fluid barrier.

The work of Dr. Neymann and Dr. Heilbrunn is very interesting. The treatment of dementia paralytica with penicillin deserves all encouragement.

DR. C. A. NEYMANN, Chicago: We have little to add to what has been reported. Our discouraging results are due in part to the type of patients we chose for these therapeutic experiments. Perhaps now that we know something about the dosage and the immediate acute action of the drug, we can treat patients who are not quite so deteriorated.

In the future, it may be possible to employ a mordant similar to the substances used in the dyeing industry. We may be able to find a substance in which the penicillin is soluble and which, in turn, is soluble in lipids. If such a drug can be discovered, something may be accomplished with the intravenous use of penicillin. This substance simply does not penetrate the deeper layers of the parenchyma of the brain.

DR. GERT HEILBRUNN, Manteno, Ill.: In answer to Dr. Gerty, I regret that no urinalyses for the excretion of penicillin were performed. Such a study would have been particularly informative in tracing the elimination of the intrathecally administered substance. The intracisternal route was chosen to bring the drug into the most immediate contact with the brain.

I followed Dr. Gronner's discussion with great interest; especially was I glad to learn that the clinical improvement and changes in the spinal fluid of his patients corroborated our own observations. However, we did not see any amelioration of neurologic symptoms, as reported by Dr. Gronner. One of our patients, with rather typical signs of involvement of the posterior column, still has absence of the knee and ankle reflexes, a positive Abadie sign and considerable disturbance of position and vibration sense.

Dr. Gronner's favorable results and Dr. Gerty's encouraging words are a stimulus to us to continue our search for a short and effective chemotherapy for dementia paralytica.

### Common Factors Precipitating Mental Symptoms in the Aged.

DR. LOREN W. AVERY, Chicago.

The appearance of mental symptoms in the aged is a matter of great concern both to the physician and to the family. The tendency is for such symptoms to be looked on as an expression of senility, from which no relief may be expected. While this is frequently true, it is important to evaluate each patient's condition carefully before a poor prognosis is given. Elderly patients are especially vulnerable to toxic states, which even in the young precipitate mental symptoms. This report concerns 22 aged patients who first manifested mental changes while under medical care. The majority of them were under observation in the hospital. The psychotic manifestations were clinically those of disorientation, confusion and memory defect. Delusions and hallucinations were observed. Since these patients recovered, it is evident that they did not suffer from senility.

Hospitalization in itself may precipitate marked mental confusion, which is especially apparent at night. The confinement of the patient to a strange room in unfamiliar surroundings, frequently amounting to solitary confinement, may result in confusion. On the other hand, hospitalization in the ward more rarely is followed by such symptoms. The removal of the patient to the home nearly always results in disappearance of the confusion.

The injudicious use of sedation is a common factor in the precipitation of mental symptoms in the aged. A noisy and unmanageable patient is disturbing, whether in the home or in the hospital. The desire for nocturnal quiet is frequently responsible for the use of sedatives. The elderly patient may be given a therapeutic dose of a sedative without danger. The danger arises when it is found that such a dose has no effect and the physician attempts to gain his objective by increasing the dose. It should be borne in mind that confused and noisy states may be delirium and may be aggravated by toxic doses of sedatives. It was found that many elderly patients recovered quickly from their mental symptoms when administration of the sedative was stopped, and a stimulant was substituted.

Disturbed mental states were found frequently to follow diseases of the respiratory system, especially bronchitis. Continued confinement to bed or to the house was probably a factor. Return to activity as soon as advisable usually resulted in recovery.

Disease of the heart frequently precipitates confused states in the elderly. Patients with cardiovascular disorders may suffer from a relative histanoxia of the brain. This is a toxic state, and the addition of toxic doses of a sedative may greatly enhance the effect of the circulatory disorder of the brain.

Elderly patients need to be guarded from confinement and from overmedication. They should be kept in their home surroundings as much as possible, and great effort should be made to maintain all possible activity.

#### DISCUSSION

DR. JOSEPH A. LUHAN, Chicago: Dr. David Rothschild, of Worcester, Mass., in a number of clinical and neuropathologic studies, has considered the problem whether the amount and situation of damage to the brain, as disclosed by anatomically demonstrable cerebral lesions associated with aging processes, could satisfactorily explain the mental symptoms in cases of psychoses with arteriosclerosis and senility. He found, especially in the arteriosclerotic group, numerous inconsistencies between the extent of the cerebral lesions and the severity of the mental symptoms—both disturbance of behavior with little demonstrable neuropathologic change and mild mental alterations with severe cerebral damage. I myself have been impressed for years with the observation at autopsy of severe cerebral arteriosclerosis in general hospital patients who had shown no obvious mental disorder. With the lengthening of the life span, through the advance and application of medical knowledge, especially in the control and treatment of infectious diseases, the degenerative disease processes and geriatric psychiatry will assume increasing importance. Yet it has been common practice in state hospitals to accept, without staff presentation or review, the diagnosis of psychosis with cerebral arteriosclerosis or senility made on the patient's admission since these illnesses connote a progressive course and hopeless outcome. Apparently, however, functional or recoverable psychoses may occur in older people. Most physicians have encountered psychoses, especially toxic-delirious states, in older people, as well as episodes with an affective or schizophrenic reaction pattern followed by practical recovery, which, because of the age of the patient or the presence of arteriosclerosis, with or without hypertension, were diagnosed as senile or arteriosclerotic in type. With

the presence of dementia, the diagnosis of senile or arteriosclerotic psychosis is justifiable, although in the acute confusional behavior of a toxic-delirious reaction the determination whether dementia is obscured or concealed by the psychosis may have to await the natural evolution of the illness.

Just as in Rothschild's opinion, persons who are handicapped psychologically (in their personality make-up or by unusual situational strains) are highly vulnerable to arteriosclerotic psychosis, so senile and arteriosclerotic persons are more vulnerable to situational and toxic influences. However, the prognosis for the latter is often better than the connotation which the diagnosis of senile and arteriosclerotic psychosis carries. In the interests of scientific nosology, the present classifications of psychoses with cerebral arteriosclerosis and senility should be reevaluated.

As a case in point, I recall an instance in which I was called to see a 66 year old retired, successful industrialist who had become overtly psychotic about three weeks after an automobile accident in which he had suffered minor physical injuries without any evidence of head injury, but as a result of which his wife was seriously injured. He appeared restless, agitated and fearful and said that the Catholic sisters in the hospital put him under hypnotic influences and that his son-in-law had tried to kill him. He feared that his food was being poisoned. He was largely disoriented for time. There was considerable retinal arteriosclerosis; the blood pressure was 170 systolic and 90 diastolic, and the deep reflexes were greatly exaggerated. He had shown tremor of the hands for the past two years. There was a history of abnormal forgetfulness for recent events of several months' duration. I made a diagnosis of psychosis with cerebral arteriosclerosis. Since the patient had been given bromides in moderate doses by his family physician, the blood was subsequently examined for bromides and found to contain 165 mg. of sodium bromide per hundred cubic centimeters. The patient recovered from his overt psychotic reaction in a month. This occurred early in 1938, and the man has remained practically well since and able to manage his own affairs. This case represents a toxic reaction to bromides in an arteriosclerotic setting.

Then there are the cases like that of a woman aged 56, first examined early in 1943, who then had evanescent focal neurologic manifestations of hypertensive and arteriosclerotic encephalopathy, with a blood pressure of about 250 systolic and 140 diastolic. She had a history of hypertension, with a systolic blood pressure reaching to 290 mm. during the preceding five years. She subsequently became obviously psychotic with a depression, for the first time in her life, early in 1943, and recovered after eight electric shock treatments. At present she is apparently mentally well, manages her home and does her own housework, although the blood pressure has not diminished. Is this case one of psychosis with cerebral arteriosclerosis?

DR. VICTOR GONDA, Chicago: Dr. Avery is to be congratulated on bringing up this important subject. In contradistinction to his observations, one must consider the fact that many elderly patients manifest psychotic symptoms in their homes, where they often become unmanageable. As soon as they are hospitalized, their symptoms disappear, with or without the use of sedatives.

There are also patients with senile dementia who show extreme restlessness or signs of tormenting anxiety, making their lives and those of their relatives miserable. Hospitalization is necessary, and despite increasingly large doses of sedatives the patient's condition remains unchanged. It is heart breaking to witness the mental sufferings. These patients are usually of advanced age, with hypertension and unmistakable signs of arteriosclerosis.

One hesitates to use electrically induced convulsive therapy with these patients. However, I can recall several instances in which the convulsive treatment eliminated the mental agony. There was left, perhaps, a person who appeared calm but was demented, or, as in another instance, the patient became socially adjusted and was able to perform some type of work for many years. An illustrative case follows:

A patient aged 74, the mother of 6 healthy sons, gradually manifested all the classic signs of senile dementia. This condition soon became complicated with a morbid fear complex, namely, that her sons would be run over by a vehicle. For two years, all day and most of the night, she stood in horror at the window of her home, watching for the "impending death" of her sons. She became greatly emaciated; because of her precarious condition and the presence of arteriosclerosis, we hesitated to give the convulsive treatment, explaining the dangers to the members of her family. The children, however, among them highly educated men, gave their permission, knowing that some serious complication might occur. A short series of electrically induced convulsions completely removed the anxiety syndrome. No complications ensued, and for all practical purposes the patient is healthy and has performed her household duties for the last three years. Her arteriosclerosis is still present.

I could cite many similar cases. This discussion should impress members of the medical profession with the fact that in cases of seemingly hopeless "senile dementia" one cannot predict which symptoms can be removed and that in such cases the convulsive shock treatment is worth a trial, in the hope that the mental suffering of the patient will be eliminated.

DR. MEYER SOLOMON, Chicago: I was glad to hear Dr. Avery's paper, based on his sound clinical experience.

I believe that in the diagnosis of mental conditions in aged persons, psychiatrists have too frequently been pessimistic and have destroyed the morale of the patient and of the family without foundation.

There is a tendency when a patient is in the 60's or 70's to diagnose his mental disorder, offhand, as senile dementia. In my own practice I have held firmly to the view that even if the patient is 70 or 75 years of age his condition is not necessarily due to senile changes in the brain.

Although in a certain number of cases such disorders are due to organic disease of the brain, one should be careful in making the diagnosis of senile dementia and should be especially careful in giving a bad or a hopeless prognosis too quickly.

It is questionable whether the term "senile dementia" should not be eliminated. Even if the aged person has a progressive deteriorating psychosis, it seems to me that it would be better to use the term "progressive geriopsychosis." A geriopsychosis may be progressive or nonprogressive.

Two illustrative cases support Dr. Avery's conclusions.

About two years ago a physician called me in consultation to see a patient whose psychosis he had diagnosed as senile dementia and whom it was desired to have committed to a state hospital. The patient was confused; he staggered about, had fallen out of bed and was irritable and noisy. The history showed

clearly that he had had transient insomnia and had been placed under treatment with large doses of phenobarbital and that his condition was probably phenobarbital intoxication. Phenobarbital medication was discontinued, and the symptoms cleared up quickly.

In contrast, I was called recently to see a patient whose psychosis also had been diagnosed as senile dementia. In looking over the hospital record carefully, I found that the patient had had a period of insomnia, due to a number of factors, and that the poor sleep had produced an exhaustion psychosis. She had been placed under treatment with small and inefficient doses of a hypnotic. She was then given sufficiently large doses of a hypnotic to insure sound sleep; in about a week her condition had cleared up, and she was transferred to a home for convalescents.

Often the treatment becomes the disease. The patient is upset; excessive doses of a medicament are given, with resulting mental confusion, and a vicious circle results. It is well to remember that aged persons may have mental disorders, such as toxic conditions and cerebral tumor.

Important, and often overlooked in aged persons, are nonorganic psychoses due to emotional problems centered about poverty, lack of a suitable home, lack of attention and love, lack of occupation and goals and a host of similar psychologic factors.

In addition to the use of any medication indicated, these personal problems must be considered and attempts made to solve them.

We psychiatrists need to make a careful reevaluation of our attitudes toward old people and of the too hurried diagnosis and management of their mental disorders.

DR. LOREN AVERY, Chicago: I wish to thank Dr. Luhan, Dr. Solomon and Dr. Gonda. I think that a careful study of such patients would show that they suffered from delirium. Because of their age, this delirium took on the characteristics of senility. Dr. Solomon brought up the important question of the emotional needs of the aged person. The worst problem for the aged is the lack of anticipation. If he is able to live as though life were endless and continues to plan and to anticipate the future, he is much less likely to suffer mental changes. His ability to live in this manner depends, of course, on his physical equipment and on the responsibilities placed on him.

Dr. Gonda raises the question of whether or not the mental symptoms returned. Of the 22 patients, I was able to follow 17. Eight of them later suffered from a typical dementia and died. Four patients are known to be living and do not show serious senile changes. One patient died of cardiovascular disease with pneumonia.

Arteriosclerosis has been considered the cause of many of the mental changes seen in the aged. It is wise to remember that arteriosclerosis is the privilege of the aged and is not necessarily the basis of their illness.

### Hysterical Convulsions Treated with Hypnosis and Psychotherapy: Report of a Case.

DR. BORIS URY, Chicago.

A 17 year old white girl was first seen in the dispensary of the Illinois Neuropsychiatric Institute in May 1944. The presenting symptom was a generalized muscular disorder in which the patient would lift her pelvis from the chair in a jerking movement. The movement would then radiate through the entire body, throwing her arms and legs outward. These movements had no athetoid or choreiform characteristics and occurred rhythmically at regular intervals. They were not under the patient's conscious control, and there was a history that the disturbance became greatly intensified under any emotional stress.

According to the history given by the family, these movements had begun in September 1943 and had become increasingly severe since that time. Because of her illness, she could not go to school, was excluded from most social activities and, for the last nine months preceding admission, had been kept in bed for supposed chorea.

Since the examination on her admission disclosed no indication of organic disease, the patient was hospitalized with the tentative diagnosis of conversion hysteria. More extensive hospitalization in the ward supported the diagnosis made on admission. Despite the history of chorea, the electrocardiogram was within normal limits. The results of electroencephalographic studies were also normal.

One week after her admission, exploration with sodium amytal revealed the more superficial psychodynamics of the illness. There was much conflict over sexuality, and the patient then revealed that in her behavior she was reacting to specific bodily sensations. As she described it, this sensation was "a funny sensation at the bottom of my spine which goes between my legs. It feels like it is going to be a tickle, but it isn't." The patient then revealed her rigid and distorted ideas concerning sexuality. She denied having any knowledge of the mechanics of the sexual act and thought that pregnancy could be induced by kissing. The patient also discussed her strict moral code. She did not believe in smoking, drinking or dancing, since these were interdicted by her religious beliefs. The patient and her family belonged to a conservative Baptist church, where the minister frequently preached sermons in which the previously mentioned activities were denounced as sinful. In addition, there was a verified history that the patient had been molested several years earlier by an elderly man with evident sexual intent.

At the conclusion of the initial exploration with sodium amytal, the patient exhibited a severe emotional disturbance with pronounced activation of the muscular symptoms. There was much pelvic movement, interspersed with episodes in which the patient assumed the classic *arc de circle* of Charcot. It was at this point that hypnotic suggestion was used to control the patient, with subsidence of the somatic and emotional symptoms.

Therapy was later continued with the combined use of hypnosis and free association, in which much of the dynamic material previously suggested was worked over in greater detail. Finally, the patient became sufficiently confident in her relation to the therapeutist to introduce a new emotional motif, which was to become increasingly important. This concerned her anger and resentment against her home situation, which had barred her from many of the social activities usual to a girl of her age and status.

Beginning on June 19, the patient's behavior changed markedly. Previous to this, she had been presented before several classes, where her convulsive disorder was reproduced by hypnotic suggestion. At this time the patient became more and more disturbed, and this disturbance was manifested by spontaneous return of the motor symptoms. On June 23 there developed a major hysterical episode, the content of which was of unusual theoretic interest. The patient's motor symptoms resembled status epilepticus. There were gross and rhymthic jerkings of the arms and legs, opisthotonos

and respiratory arrest. Nevertheless, it was interesting to observe that there was no true extensor rigidity and no tonic and clonic phase and that during the rigidity the arms were kept flexed across the chest. There were no synchronous dilatation of the pupils, no loss of the corneal reflex, no Babinski sign and no cyanosis. Judged by her responses, the patient was in a semi-detached state, with partial consciousness of her acting out.

It was noted that any attempt to bring the symptoms under control only aggravated their intensity. The patient was placed in a tub, where she thrashed about violently, splashing every one in the vicinity. It was therefore decided to bring her under control by hypnotic suggestion.

This process lasted about an hour and a half, during which an interesting sequence of events was revealed. Under constant hypnotic suggestion reenforced by slow massage of the eyeballs, the symptoms of the "epileptic type of seizure" gradually became less intense. As the affect began to subside and she became more conscious, the aggressiveness and temper tantrums became more evident. The patient's expression became a clear picture of primitive hate and rage. She made rage sounds, such as incomplete articulations, and the movements became disorganized from their "epileptic character" and were more and more an aimless thrashing about. Finally, after about an hour and a half, the patient became completely quiet, and her face assumed an almost beatific expression of pure dependence and passivity. Her face became smooth, calm and childlike. Before this stage was reached, she expressed her resentment at having her will broken by that of the therapeutist by several times bursting into tears, especially when supraorbital pressure was applied to stop the convulsive movements.

The patient was then removed from a hypnotic state and psychotherapy initiated with the patient fully conscious. Following the cue given by the patient's behavior, the psychiatrist encouraged her to verbalize her various resentments. The patient then revealed the fact that she had been seen by her mother two days previously, who had stated, "I do not want you to come home as long as you are jerking; I want you to stay here even if it takes a year." The patient reacted to this with much resentment. She also felt frustrated in not receiving as much attention from the therapeutist as previously. The psychiatrist was now able to bring out much of her resentment against her home environment, where all forms of amusement, such as dancing, shows and easy social relations between young people, were interdicted on the basis of religious teachings.

After this episode, there occurred minor repetitions of similar disturbances, which gradually subsided by virtue of the more consistent psychotherapy, which, as before, combined hypnosis and free association. On July 14 the patient's second sister died of tuberculosis, and after this the patient presented a dream which seemed related to the basic mechanisms involved in the determination of the form of the illness. This involved the patient's unconscious manipulation of her "body image."

"I dreamt that my sister was dead. She was lying in a coffin; then she began to pop up like she was playing 'peek-a-boo.' I knew she was dead, but she was still active. The feeling I have about this is that the person may be dead but the muscular movements go on." The patient here symbolized the dissociation of the conscious personality from the expressive muscular movements of the body. It is obvious that this mirrored the hysterical situation. Asked to express her associations with this dream, the patient stated: "When a person is dead, their soul is gone. The soul is that part of the person which is very beautiful, which tries to obey, which is the best part of you. Movements mean that the body is free, can run, jump or do what it likes. Sex is a movement, and an embrace is a movement."

The patient remained in the hospital until August. On her return to her own home and community, her adjustment showed decided improvement in that she was now sufficiently free of her disturbing muscular movements to go to school and to join in the usual social activities. There still occur occasional, moderate exacerbations under the influence of frustration, anxiety or sexual stimulation. No attempt will be made here to explore all the theoretic implications of this material, and the close resemblance of this case to some of the earlier cases of Freud is unmistakable. The dream material points to a naive, subjective concept of the body image, which certainly has some relevance to the hysterical conversion mechanism.

The prominence of rage in initiating hysterical convulsions has previously been noted by psychiatrists, who, however, on the basis of this association, have tended to interpret the genuine organic epileptic discharge as basically a rage reaction. It is a clinical fact that any affective stimulus, whether it be rage or fear, or even music, may precipitate an epileptic attack in a person who possesses the pathophysiologic mechanism. Certainly, in this patient the extreme of rage did not precipitate any organic epileptic reaction, evidence in favor of the conclusion that rage itself cannot create the essential epileptic discharge but can only influence the threshold, a possibility which, however, does not justify the equating of convulsive disorder with rage per se.

### DISCUSSION

DR. MEYER SOLOMON, Chicago: I wonder whether there is not a tendency to resort too often to the more indirect and circuitous methods of examination, represented by so-called free association, so-called dream interpretation, hypnosis and barbiturates. For example, I have not been convinced that in the average case one can get any more information by studying a patient's dreams than by talking directly with him about his personal problems. In other words, is it not true that by using the direct method of approach one can in most cases get the information one needs? Frank discussion with the family and with the patient is, in most instances, quite sufficient to get the data required in ordinary clinical practice.

I do not feel that the dream interpretations given by Dr. Ury have really been proved to be correct. May one not have arrived at the heart of the problem in this case much more readily and accurately by the direct method of approach than by the indirect technics employed?

DR. C. A. NEYMANN, Chicago: Hypnosis has been employed on a larger or smaller scale ever since the days of Mesmer. It is generally recognized that the depth of hypnosis varies greatly. Physicians who have employed hypnosis frequently demand deep hypnosis to accomplish therapeutic results. The first question would, therefore, be the depth of the hypnosis. I do not consider hypnosis very deep unless the patient is absolutely anesthetic to pinprick and to more serious trauma. A thoroughly hypnotized patient can usually be taught to blanch an arm or to produce goose flesh of an extremity voluntarily and will be bent to the hypnotist's will to

the point where posthypnotic suggestion can be employed. However, such posthypnotic suggestions are evanescent. The patient soon forgets these suggestions and falls back into his former reaction type. Hypnosis has, therefore, often proved to be therapeutically inefficient, if not worthless.

At present, the only real medical value of this procedure seems to be in helping the patient to recover from a deep hysterical amnesia or from a hysterical aphonia. Such symptoms are in themselves so troublesome that it is valuable and proper to treat the patient in this manner in order to produce even temporary recovery. This, of course, has nothing to do with the underlying reaction type. Usually patients who have recovered from hysterical amnesia or aphonia either have another episode in a short period or produce other symptoms which make life just as difficult for them. It would seem that the employment of psychoanalysis together with hypnosis might be indicated for such a patient. In my experience, an exploratory hypnosis brings to light only problems which are very near the conscious level and are not buried in the deeper subconscious strata of the mind.

DR. FRANCIS GERTY, Chicago: If one wishes to have a shrub grow, one prunes it by cutting it back, and it seems that this happens with hysteria too. The more it is cut back superficially, the stronger it becomes. Of course, one is anxious to find a short, successful and lasting treatment for hysteria. In most attempts to find the short cut, however, it seems that immediate results of only temporary duration are secured. And almost always in a search for a short cut to the successful treatment of hysteria, one finds that hypnosis is included. I suppose that practically every physician here has at some time or other hypnotized a patient. Some have hypnotized a great many patients. In spite of this, and in spite of the fact that much has been written on hypnotism in the last one hundred and fifty years, from Mesmer to Freud, one still knows practically nothing about the internal processes concerned with the state of being hypnotized. One finds great difficulty in using it with any real measure of success in the treatment of patients. It is true that one can get results, as I have pointed out before, but they are only temporary. Freud, using hypnotism, started out with the idea of unearthing material that might help in understanding the mechanism that lay behind hysteria. He gave up the method because he thought that other means were better. Now, the only advantage that hypnosis could have, it seems to me, would be to save time. Certainly, one does not gain all of the information one wishes in the hypnotic state. Sooner or later one must drop the hypnotic part of the treatment in favor of something else. I must confine my discussion to that aspect of the matter, rather than consider the success of the method. Dr. Ury states that the girl is not cured yet. Expectation of that must be postponed to the future. He has gained some interesting information and probably could have gained that information without the hypnosis. In the process of doing this, he has probably learned much about hypnosis, but, in common with most physicians and psychiatrists of the past, I assume he has not learned much about hypnosis as it concerns the internal goings-on during the state of hypnosis.

DR. BORIS URY, Chicago: I want to thank all the discussants, and I think that everything that has been said was relevant to the problems of the case.

As to the depth of the hypnosis employed, I can only state that it was sufficient to control the symptoms, which were severe. As Dr. Gerty had stated, the situation seemed to be of an emergency nature. After all, patients have died from the somatic repercussions of a sustained hysterical disorder, and this girl was suspected of having a cardiac disorder, even if there were no frank signs of heart disease. Treatment of the acute state seemed limited to heavy sedation or hypnosis. I chose hypnosis because I thought it could be fitted into the total psychotherapeutic pattern.

Why I did not get more significant material in the hypnotic state I do not know. It may be a point of technic. It was my impression that in this case the nonhypnotic parts of the therapy were limited by the peculiar emotional configuration. I felt that the affect contained within the ego and accessible to the conscious personality was extremely thin. It was as though one encountered a structure made of tissue paper. There was no resistant structure with which one could interact so as to "work out" the conflict at a conscious level. Most of the affect seemed to be retained within the subconscious areas of the personality. This affect remained internalized and self cohesive but was released during the hysterical episodes. There remains the problem of tapping this reservoir of affect in the usual psychotherapeutic relationship. It is possible that this could be done more successfully by a woman therapeutist; or, again, it may be a problem of variation in technic.

Although I am not completely satisfied with the result of treatment, the patient's condition is much improved. She is going to school, is developing her social relationships and is no longer a social outcast, nor is she confined to bed for a supposed choreic motor disorder. Of course, she is subject to relapses, but they are not so severe as the previous illness, and the level of her adjustment indicates progressive improvement.

What interests me in the hypnotic technic is the possibility that this method might help one to understand the mind-body relationship from a more physiologic point of view. After all, here is a clear case in which the physiology of the brain is altered by emotional factors. It is known that one can change the electrical activity of the occipital cortex by hypnosis. Electroencaphalographic recording from this cortex when the patient has his eyes closed gives the "Berger rhythm," a result which testifies to the internal synchrony of the visual cortex. Now if one gives such a subject hypnotic suggestion that he is seeing, the electrical rhythm changes to the usual complex form associated with actual visual activity. Obviously, the physiology of the brain has been changed by the hypnosis.

I wonder whether this is not true of some of the other properties of the hypnotic state. It used to be thought that if one suggested to a patient that his arm was insensible and then burned him with a cigaret, he felt the pain physiologically but not consciously. Is it not possible that the patient does not feel in the physiologic sense? Perhaps the hypnotically induced mechanism actually inhibits certain physiologic mechanisms. Recent neurophysiologic work has indicated the presence of a widespread, yet finely articulated, inhibitory mechanism. This can be evoked from structures as low as the reticular formation in the brain, as shown by Magoun. This mechanism has a widespread cortical representation, also, and can be evoked from many structures between these two levels. It is possible that a combination of the dynamic studies in hypnosis with neurophysiologic studies of the brain by modern methods might advance knowledge of cerebral functions and their meaning in the psychiatric syndromes.

## CHICAGO NEUROLOGICAL SOCIETY

R. P. MACKAY, M.D., *in the Chair*

*Regular Meeting, Dec. 12, 1944*

**Use of Galvanic Tetanus and the Galvanic Tetanus Ratios in Electrodiagnosis of Lesions of Peripheral Nerves.** DR. LEWIS J. POLLOCK, DR. JAMES G. GOLSETH and DR. ALEX J. ARIEFF.

It has been stated that a galvanic current is capable of producing a sustained contraction, or tetanus, of a muscle and that such a tetanic response to the galvanic current has variously been called "myotonic reaction," "galvanotonus" or "galvanic tetanization." Since, however, the tetanus results from galvanic stimulation, we propose that it be called "galvanic tetanus."

In addition, the ratio of the threshold value of current for galvanic tetanus to the rheobasis has been studied and has variously been called "polarization coefficient" or "contraction coefficient." Again, since this is the ratio of two specified values of galvanic current, we propose that the term "galvanic tetanus ratio" be adopted.

Both the threshold values of current for galvanic tetani and, in particular, the galvanic tetanus ratios give reliable information regarding the state of a muscle. Because of this, it is thought unwise to consider galvanic tetanus as simply one of the characteristic changes in the mode of contraction of muscle.

It should be pointed out at this time that the presence of edema fluid in the subcutaneous tissues may cause the rheobases and, similarly, the threshold values of current for galvanic tetani of even a denervated muscle to be exceedingly high. For this reason, one should be reluctant to make the diagnosis on these high values of current alone. In such a case of denervation, however, with accompanying edema of the subcutaneous tissues, one would find that even though these values of current are abnormally high the galvanic tetanus ratios would be either at or close to unity.

Attention is called to the fact that the response of muscle to either strong galvanic currents or progressive currents of long duration is tetanic. Similarly, the changes in these two types of stimulation, and in particular the changes in their respective ratios, parallel one another during the periods of degeneration, denervation and regeneration.

The characteristics of denervated muscle have been shown to be low rheobases, low threshold values of current for galvanic tetani and galvanic tetanus ratios either approaching or at unity. Conversely, the characteristics of regenerating muscle have been shown to be high rheobases, high threshold values of current for galvanic tetani and tetanus ratios which are rather large multiples of 1.

It follows, therefore, that when a sufficiently long period has elapsed after nerve injury or suture for the muscle to have become denervated (forty-five to sixty days) and examination with the galvanic current shows (1) high rheobases, (2) high threshold values of current for galvanic tetani and (3) high galvanic tetanus ratios, one may be certain that the muscle in question is not denervated but is regenerating.

When, on the other hand, a sufficiently long period has elapsed after nerve injury or suture for the muscle to be regenerating (ninety or more days) and examination with galvanic stimulation shows (1) low rheobases, (2) low threshold values of current for galvanic tetani and (3) low galvanic tetanus ratios, one may conclude that the muscle in question is not regenerating but that, on the other hand, it is denervated and that surgical intervention is indicated.

This paper will be published in full in *Surgery, Gynecology and Obstetrics* (**81**:660 [Dec.] 1945).

**Histopathologic Characteristics of Progressive Muscular Atrophy.** DR. GEORGE B. HASSIN, Chicago, and DR. WILLIAM DUBLIN, Los Angeles.

Progressive muscular atrophy (myelopathic muscular atrophy), Duchenne-Aran type, is not a morbid entity but a component or a partial manifestation, as it were, of amyotrophic lateral sclerosis. Its clinical features—*progressive muscular wasting, usually beginning in the* hands, and unassociated with pain or sensory, genitourinary or trophic disturbances—become sooner or later complicated by bulbar and corticospinal signs, resulting in an unmistakable picture of amyotrophic lateral sclerosis. On the whole, the Duchenne-Aran form of progressive muscular atrophy is rare, and its pathologic picture has not been extensively studied. This is especially true of the condition of the muscles, to which particular attention has been paid in the study of the present case. A man aged 66 was admitted to the Pierce County Hospital, Tacoma, Wash., because of difficulty in breathing and swallowing, of four days' duration. He gave a history of general weakness and muscular wasting of four years' duration. The wasting was pronounced in the hands; the muscular tone was lost, and the tendon reflexes were absent; sensibility apparently was not disturbed. Because of the patient's precarious condition, which resulted in death twenty-four hours after his admission, serologic and other detailed laboratory examinations could not be made.

Necropsy revealed no gross changes in the brain or viscera except for cerebral edema and arteriosclerosis in the brain, kidneys and heart. The microscopic changes were as follows: reduced number of myelin fibers and ganglion cells in the ventral horns of the spinal cord, especially in the cervical and thoracic regions; mild neuroglial and microglial reactions, which were somewhat more in evidence in the white substance of the spinal cord, such as the areas of the pyramidal tracts; multiple hemorrhages in the medulla oblongata, obviously agonal, without reactive phenomena or parenchymatous cell changes; fragmentation of some cells, with formation of globules (sarcolytes); invasion of the fragmented muscle tissue by myophages (histiocytes); formation of vacuoles, harboring nuclei of indefinite origin; fatty degeneration of some muscle fibers; occasional mild proliferation of the endomysium and vascular changes in the form of endarteritis obliterans, and numerous amyloid bodies in both the gray and the white substance. In respect to many features, the changes in the muscles resembled those seen in nerve fibers undergoing degeneration and in cases of progressive muscular dystrophy. In the latter condition, however, lipomatosis and multiple connective tissue scars are the outstanding features. The endarteritis and the loss of the tendon reflexes in this case suggest syphilis as the possible cause of the atrophy, although endarteritis obliterans also occurs in arteriosclerosis, rheumatic fever and tuberculosis and the absence of tendon reflexes may have been due to the moribund condition of the patient.

**The Dynamic Visual Field.** DR. WARD C. HALSTEAD.

# Book Reviews

**Psychology of Women: Motherhood. Volume II.** By Helene Deutsch, M.D. Price, $5. Pp. 498. New York: Grune & Stratton, Inc., 1945.

This book on motherhood by Helene Deutsch is the second volume of her study of the psychology of women. The first volume deals with girlhood and the female psyche from infancy to the age of adolescence. In the second volume the author gives a detailed psychoanalytic study of the essential successive life phases connected with reproductive activity of the mature woman. The complicated psychobiologic interrelationship of all stages of the reproductive function frequently leads to pathologic psychosomatic manifestations. These disturbances are often discussed and mentioned. The main emphasis, however, is placed on the demonstration of the normal female psyche.

In the first chapter the biologic and social aspects of motherhood in different cultures and societies are briefly presented. The subsequent chapters deal with the relation of motherhood and sexuality, the psychology of the sexual act, conception, pregnancy, delivery and confinement, and the first mother-child relationship. In the epilogue the period of climacterium is discussed.

Helene Deutsch distinguishes between motherhood and motherliness: "Motherhood refers to the relationship of the mother to her child as a sociologic, physiologic and emotional whole. Motherliness is a definite quality of character that stamps the woman's whole personality and is an emotional phenomenon that seems to be based on the child's need for care and its helplessness." She stresses therefore that the two types of the motherly and the unmotherly woman are not related to the fact of childbirth.

The relations between sexuality and motherliness are of a complicated nature—sometimes in harmony, at other times in disaccord—thus leading to different patterns of personality. The infantile concept of motherhood, the birth process, pregnancy, the sexual act, etc., supply the pattern for the later psychophysical aspects of motherhood in the mature woman. The great influence of unconscious trends on incidents of sterility, conception and abortion is demonstrated. The extent to which the periods of pregnancy and delivery are under the impact of psychic forces and the degree to which feelings of guilt and narcissistic, masochistic, destructive and other tendencies play a role during the course of pregnancy and delivery are emphasized.

After the physical separation of mother and child the two are reunited through the formation of a new and strong tie, which the author calls the "psychic umbilical cord." The motherly woman reaches this harmony with her offspring by directly identifying herself with the child. The growing mother-child relationship is influenced from the beginning by various psychologic forces from the mother's own childhood and environment.

The period of confinement assists the mother in overcoming the trauma of the physical separation from her child. The difficulties which may arise in connection with lactation and weaning are considered by the author to be largely of psychogenic origin.

In the discussion of the problem of unmarried mothers and illegitimate pregnancies, one is shown different types of illegitimate motherhood and the social and psychologic motives which may be present, such as passive masochistic trends, narcissistic and aggressive tendencies or the need for tenderness.

The time of the climacteric includes the last phase of motherhood, the period of grandmotherhood. The motherly woman receives this gratification at that time of her life which is otherwise under the impact of serious narcissistic frustrations. This dangerous age is called the time of "second puberty," in which the aging woman repeats her psychologic adolescence. By various methods of sublimation, such as social activities and flight into fantasy, the woman fights against the biologic trauma of that period.

The author illustrates her material by numerous examples taken from case histories and the psychiatric and anthropologic literature. The information presented is taken to a large extent from the author's own clinical experiences. Based on the fundamental principles and concepts of psychoanalysis, her findings shed new light on the feminine psychologic structure and show how the inner dynamic forces are of great importance in the life of the woman and mother. Of special interest is the understanding of the woman in the climacteric and of the adoptive mother, the latter having largely been neglected from the psychologic standpoint. This book is highly recommended as a valuable contribution.

**A Bibliography of Visual Literature, 1939-1944.** Compiled by John Fulton, Phebe M. Hoff and Henrietta T. Perkins. Prepared for the Committee on Aviation Medicine, Division of Medical Sciences, National Research Council Acting for the Committee on Medical Research, Office of Scientific Research and Development, Washington, D. C. Price, $3. Pp. 117. Springfield, Ill.: Charles C Thomas, Publisher, 1945.

The work of compiling this important bibliography was stimulated by the war. It was initially requested by the British Air Ministry, through its Flying Personnel Research Committee, and was subsequently done under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Yale University.

The eye and vision have always been important in protecting man from his enemies. This is especially true in times of war. Moreover, the use of airplanes as an instrument of offensive strategy and the use of black-outs have obliged people to use their eyes under adverse and various circumstances.

This important bibliography considers visual literature under the headings of (1) anatomy and ophthalmology; (2) the physiology and psychology of vision as they are concerned with visual examination and testing; (3) the importance of ocular defects in military personnel; (4) ocular trauma in military service; (5) problems of ocular protection and goggles, and (6) the problems of illumination and visibility.

All this literature is carefully collected, and the work undoubtedly has been, and will continue to be, of great value to any person interested in the problems of vision. The volume is highly recommended as an excellent bibliography on this important subject.

Archives of Neurology and Psychiatry

VOLUME 54 NOVEMBER-DECEMBER NUMBER 5



# ANTICONVULSANT ACTIVITY OF SULFOXIDES AND SULFONES

H. HOUSTON MERRITT, M.D.

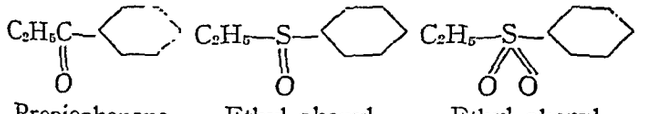
TRACY J. PUTNAM, M.D.

AND

W. G. BYWATER, PH.D.

NEW YORK

Certain anticonvulsant sulfur compounds which were mentioned briefly in a previous publication [1] have been investigated in more detail. Interest in the possible anticonvulsant properties of the sulfoxides and sulfones was suggested by their structural similarity to the ketones, which had been found to have pronounced anticonvulsant activity.[2] These structural relationships are illustrated by the formula for ethyl phenyl ketone (propiophenone), ethyl phenyl sulfoxide and ethyl phenyl sulfone:



Propiophenone — Ethyl phenyl sulfoxide — Ethyl phenyl sulfone

The sulfoxides and sulfones possess more desirable physical properties than the alkylaryl sulfides, which were also observed to possess anticonvulsant activity. Additional study of homologous sulfides was discontinued because of their undesirable odor and unsavory taste. Our interest in the sulfones was further stimulated by the observation that dimethyl sulfone occurs naturally.

Thus, Pfiffner and North [3] isolated it from adrenal gland extracts, while Ruzicka and coworkers [4] reported its isolation from dried cattle blood. Although this sulfone could arise from the metabolism of other naturally occurring sulfur-containing bodies, its occurrence in the animal organism aroused our curiosity about its possible biologic significance. It is also interesting to note that bis-β-hydroxyethyl sulfoxide has been found in adrenal gland extracts.[5]

## EXPERIMENTAL STUDY

*Method.*—The sulfoxides and sulfones described in tables 1 and 2 were tested in cats by the method previously described.[6] All the drugs were administered orally either in capsules or, if liquid, by stomach tube. The strength of current necessary to produce a convulsion was determined immediately before and approximately two hours after administration of the compound. The convulsive threshold for cats weighing 2 to 4 Kg. was usually 15 to 25 milliamperes. After administration of an effective anticonvulsant, such as diphenylhydantoin sodium or phenobarbital, this threshold was raised to over 50 milliamperes. In order to conserve animals, stimulations with currents in excess of 50 milliamperes were not given. The anticonvulsant action of a compound was rated for a particular dose as follows:

O..No change in convulsive threshold

+..Elevation of convulsive threshold 5 to 15 milliamperes

++..Elevation of convulsive threshold 20 to 30 milliamperes

+++..Convulsive threshold elevated to 50 milliamperes

++++..Convulsive threshold elevated to more than 50 milliamperes (i. e., no convulsion obtained when stimulated with 50 milliamperes)

In each instance tests were made at more than one level. When the compound was inactive, only the highest dose employed in the tests is

From the Department of Neurology, Columbia University College of Physicians and Surgeons; the Montefiore Hospital; the New York Neurological Institute, and the Research Laboratories of Parke, Davis & Company.

1. Putnam, T. J., and Merritt, H. H.: Chemistry of Anticonvulsant Drugs, Arch. Neurol. & Psychiat. **45**:505-516 (March) 1941.

2. (*a*) Merritt, H. H., and Putnam, T. J.: A New Series of Anticonvulsant Drugs Tested by Experiments on Animals, Arch. Neurol. & Psychiat. **39**:1003-1015 (May) 1938. (*b*) Putnam and Merritt.[1]

3. Pfiffner, J. J., and North, H. B.: Dimethyl Sulfone: A Constituent of the Adrenal Gland, J. Biol. Chem. **134**:781, 1940.

4. Ruzicka, L.; Goldberg, M. W., and Meister, H.: Inhaltsstoffe des Blutes: Isolierung von Dimethyl-Sulfon aus Rinderblut, Helvet. chim. acta **23**:559-561, 1940.

5. Reichstein, T.: Ueber Cortin, das Hormon der Nebennierenrind, Helvet. chim. acta **19**:41, 1936. Reichstein, T., and Goldschmidt: Ueber die Bestandteile der Nebennierenrinde: III. Die schwefelhaltige Körper, ibid. **19**:401-402, 1936.

6. Putnam, T. J., and Merritt, H. H.: Experimental Determination of the Anticonvulsant Properties of Some Phenyl Derivatives, Science **85**:525-526, 1937. Merritt and Putnam.[2a]

reported. The dose giving a ++++ response for the active compound is recorded, toxicity permitting. A typical example of the ranges in doses is given for *p,p'*-diaminodiphenyl sulfone and its diacetyl derivative.

TABLE 1.—*Anticonvulsant Activity of Sulfoxides (RSOR')*

| R | R' | Anticonvulsant Activity | Dose, Mg./Kg. |
|---|---|---|---|
| Ethyl | Phenyl | ++++ | 70 |
| n-Propyl | Phenyl | ++++ | 150 |
| Isopropyl | Phenyl | ++++ | 150 |
| Phenyl | Phenyl | 0 | 100 |
| | | 0 | 200 |
| | | + | 250* |
| p-Nitrophenyl | p-Nitrophenyl | ± | 300 |
| p-Phenetyl | p-Phenetyl | 0 | 225 |

* Toxic dose.

TABLE 2.—*Anticonvulsant Activity of Sulfones ($RSO_2R'$)*

| R | R' | Anticonvulsant Activity | Dose, Mg./Kg. |
|---|---|---|---|
| Methyl | Methyl | 0 | 70 |
| Ethyl | Ethyl | 0 | 130 |
| Ethyl | Phenyl | ++++ | 100 |
| n-Propyl | Phenyl | ++ | 520 |
| n-Dodecyl | Phenyl | 0 | 470 |
| Ethyl | o-Aminophenyl | 0 | 50 |
| Ethyl | p-Aminophenyl | + | 470 |
| n-Dodecyl | p-Aminophenyl | 0 | 450 |
| Phenyl | Phenyl | ± | 370 |
| Phenyl | p-Aminophenyl | 0 | 520 |
| p-Aminophenyl | p-Aminophenyl | 0 | 112 |
| | | 0 | 178 |
| | | + | 185 |
| | | ++++ | 227 |
| | | | 357* |
| p-Aminophenyl | m-Aminophenyl | ++ | 500 |
| p-Acetaminophenyl | p-Acetaminophenyl | 0 | 217 |
| | | 0 | 250 |
| | | 0 | 400 |
| p-Acetaminophenyl | p-Nitrophenyl | 0 | 500 |
| p-Tolyl | p-Tolyl | 0 | 260 |
| | | 0 | 800 |
| p-Aminophenyl | o-Sulfonamido-p-aminophenyl | 0 | 220 |
| p-Aminophenyl | 2-Amino-5-thiazolyl | ++++ | 170† |
| Ethyl | 2-Benzothiazyl | 0 | 70 |
| | | 0 | 150* |
| Phenyl | $CH_2CONH_2$ | 0 | 460 |
| Phenyl | $CH_2CH_2CONH_2$ | 0 | 470 |

* Lethal dose.
† Dose dissolved in diluted hydrochloric acid and administered by stomach tube.

*Results.*—Unfortunately, dimethyl sulfone was inactive in the dose tested, and the experiment did not help to elucidate the pharmacologic significance of this sulfone in the animal organism. We believe the given dose was large as compared with the probable concentration of dimethyl sulfone (about 375 mg. per thousand kilograms of dried cattle blood) [5] in the animal body and therefore some response might have been expected if the drug were acting on the mechanism involved in this anticonvulsant test.

The peak of activity in the sulfoxide and sulfone series studied occurred with the alkylaryl derivatives. Thus ethyl phenyl, propyl phenyl and isopropyl phenyl sulfoxides and the ethyl phenyl and propyl phenyl sulfones are active. The activity apparently drops off with *n*-propyl phenyl sulfone and is entirely lacking in dodecyl phenyl sulfone. Introduction of an amino group into ethyl phenyl sulfone, either in the ortho or in the para position, destroyed the activity of the parent compound.

Diphenyl sulfoxide and diphenyl sulfone were only slightly active. Introduction of one amino group into the latter compound did not increase the activity, but two amino groups symmetrically substituted results in greater activity (*p,p'*,-diaminodiphenyl sulfone). However, the diaminodiphenyl sulfone was not as active as the alkylaryl sulfoxides or ethyl phenyl sulfone.

A comparison of the more promising sulfoxides and sulfones with the corresponding ketones is shown in table 3. The figures in parentheses denote the oral dose in milligrams per kilogram at which the activity was found.

TABLE 3.—*Comparative Anticonvulsant Activities of Sulfoxides and Sulfones and Ketones**

| R | R' | Ketone | Sulfoxide | Sulfone |
|---|---|---|---|---|
| Ethyl | Phenyl | ++++ (200) | ++++ (70) | ++++ (100) |
| n-Propyl | Phenyl | ++++ (330) | ++++ (150) | ++ (520) |
| Phenyl | Phenyl | ++++ (200) | ± (250) | ± (370) |
| p-Aminophenyl | p-Aminophenyl | 0 (200) | .. | +++− (227) |

* Figures in parentheses represent the oral dose, expressed in milligrams per kilogram of body weight, at which the activity was found.

Ethyl phenyl sulfone was chosen for clinical trial because it is the most stable and easily prepared of the active drugs in this group. It does not have the sedative action of propiophenone, and, as a low-melting solid rather than a liquid, it is more easily administered. Acute and chronic toxicity studies on mice, rats and dogs show it to be somewhat more toxic than diphenylhydantoin sodium but suitable for clinical use in low doses.[7]

## CLINICAL RESULTS WITH ETHYL PHENYL SULFONE

Twenty patients refractory to other forms of treatment have been treated with ethyl phenyl sulfone for periods of one to eighteen months in doses varying from 0.2 to 1.6 Gm. per day. It can readily be seen from table 4 that ethyl phenyl sulfone was effective in the treatment of convulsive seizures in certain patients. In spite of the fairly large doses which have been used, there have been no serious untoward effects. In fact, the drug produced practically no symptoms.

CASE 1.—S. G., a 22 year old white man, had been subject to grand mal attacks and minor seizures, char-

7. Dr. O. M. Gruzhit, of Parke, Davis & Company, furnished the data on toxicity.

acterized by falling to the floor without apparent loss of consciousness, since the age of 14. Grand mal seizures occurred once every four to five days. Treatment with diphenylhydantoin sodium was started in February 1938. After a few months' treatment, the dose of this drug was increased to 0.6 Gm. a day. The number of grand mal attacks was reduced to one until early in 1940, when the minor attacks began to occur with greater frequency, until they numbered one to several daily. The addition of phenobarbital (3 grains [0.195 Gm.] a day) or phemitone (3-methyl-5-phenyl-5-ethyl barbituric acid) (6 grains [0.39 Gm.] per day) to the dose of diphenylhydantoin was not followed by any decrease in the frequency of attacks. In October 1941 ethyl phenyl sulfone, in a dose of 0.8 Gm. per day by mouth, was added to the dose of 0.5 Gm. of diphenylhydantoin sodium, and to May 1943 there were one grand mal attack and six of the minor attacks. During this period the patient had taken a job as attendant in a hospital and had worked regularly. In October 1943 the minor attacks began to recur at intervals of five to seven days, and ethyl phenyl sulfone was discontinued. While the patient was taking the drug, periodic examinations of the urine and blood gave normal results. The weight has remained stationary, and there have been no signs of a toxic effect of the drug.

CASE 2.—D. B., a 16 year old white girl had been subject to grand mal seizures since the age of 7 years. Attacks occurred about once every two to three weeks. Previously she had been treated with large doses of phenobarbital (4½ grains [0.29 Gm.] a day), diphenylhydantoin sodium (0.5 Gm. a day) and combinations of diphenylhydantoin and phenobarbital, phemitone or bromides. Treatment with ethyl phenyl sulfone, 1 Gm., and diphenylhydantoin sodium, 0.4 Gm., was started on Sept. 19, 1941. Subsequent attacks occurred February 1942, June 1942, October 1942 and April 1943. After the patient's father died, in June 1943, she was sent to a special school, where she was treated by the school physicians. During treatment with ethyl phenyl sulfone there were no signs of toxicity. Periodic blood counts and examinations of the urine gave normal results. There had been a reduction in weight from 130 to 115 pounds (65 to 57.5 Kg.), as a result of dieting for obesity.

CASE 3.—M. S., a 15 year old white girl, had been subject to grand mal seizures since the age of 14 months. These seizures occurred on an average of once a week in spite of administration of phenobarbital and bromides and a ketogenic diet. Diphenylhydantoin sodium therapy was started in December 1937 but was discontinued after the appearance of a cutaneous rash. From 1937 to 1942 the patient was treated with various combinations of diphenylhydantoin, phenobarbital, phemitone and bromides, with no appreciable reduction in the frequency of the attacks. In October 1942 treatment with ethyl phenyl sulfone, in a dose of 1 Gm. a day, and phemitone, in a dose of 0.1 to 0.2 Gm., was started. The patient had no attacks for eight weeks and only three attacks in the next three months. After this the attacks began to recur at intervals of ten to fourteen days, and ethyl phenyl sulfone was discontinued in September 1943. There were no toxic symptoms while the patient was taking the sulfur compound. The blood and urine were normal, and there was no change in weight.

TABLE 4.—*Effect of Ethyl Phenyl Sulfone on Convulsive Seizures*

| | Color | Sex | Age, Yr. | Dose, Gm. | Length of Time Administered, Months | Effect on Frequency of Seizures as Compared with Previous Forms of Treatment | General Condition of Patient | Signs of Toxicity |
|---|---|---|---|---|---|---|---|---|
| S. B. | W | M | 22 | 0.7-1.2 | 24 | Greatly decreased for 18 months | Improved | None |
| D. B. | W | F | 16 | 0.3-1.0 | 21 | Greatly decreased for 18 months | Improved | None |
| M. S. | W | F | 15 | 0.8-1.2 | 11 | Greatly decreased for 4 months | Improved | None |
| W. L. | W | M | 21 | 0.8-1.2 | 6 | Greatly decreased for 3 months; then same frequency as before | Unchanged | None |
| H. B. | W | M | 21 | 0.8-1.2 | 12 | Greatly decreased | Unchanged | None |
| F. C. | W | M | 26 | 0.6-1.0 | 5 | Unchanged | Unchanged | None |
| D. A. | N | F | 4 | 0.2-0.4 | 2 | Unchanged | Improved | None |
| E. C. | W | F | 30 | 0.2-1.0 | 4 | Slightly decreased | Unchanged | None |
| G. L. | W | M | 14 | 0.8-1.6 | 6 | Moderately decreased | Improved | Slightly ataxic on large dose |
| C. L. | W | M | 43 | 0.8-1.4 | 3 | Slightly decreased | Unchanged | Slightly ataxic on large dose |
| V. M. | W | M | 11 | 0.4-1.0 | 12 | Slightly decreased | Unchanged | Slightly ataxic on large dose |
| J. N. | W | M | 14 | 0.4-1.4 | 7 | Unchanged | Unchanged | None |
| N. P. | W | M | 7 | 0.4-0.8 | 2 | Unchanged | Unchanged | None |
| J. P. | W | M | 16 | 0.3-1.2 | 4 | Unchanged | Unchanged | Slight gastric distress |
| F. S. | W | M | 8 | 0.3-1.0 | 4 | Unchanged | Unchanged | None |
| I. W. | W | F | 35 | 0.2-1.0 | 9 | Decreased | Unchanged | None |
| S. S. | W | F | 12 | 0.5-1.0 | 1 | Unchanged | Unchanged | None |
| C. R. | W | F | 5½ | 0.2-0.6 | 1 | Unchanged | Unchanged | None |
| J. C. | W | M | 44 | 0.2-1.0 | 3 | Unchanged | Unchanged | None |
| G. E. | W | F | 12 | 0.4-1.2 | 4 | Slightly decreased | Unchanged | None |

No attempts were made to determine the effect of the drug on patients whose seizures have been controlled by either phenobarbital or diphenylhydantoin, because it was believed that any new drug should be subjected to the more severe test

first and proved to be superior to the drugs in common use in treatment of the refractory conditions before it is recommended for the less refractory ones.


## SUMMARY

A series of sulfoxide and sulfone drugs have been studied for their anticonvulsant effect in the cat, using the electric shock technic.

Ethyl phenyl sulfoxide and ethyl phenyl sulfone raise the convulsive threshold in doses comparable to the dose of propiophenone without producing a hypnotic effect.

Clinical trial of ethyl phenyl sulfone indicates that it has definite anticonvulsant activity, but this activity is not sufficiently greater than that of diphenylhydantoin sodium to recommend it for general use on the basis of the preliminary appraisal.



Mr. B. F. Tullar and Mr. L. L. Bambas prepared the sulfoxides and sulfones.



Montefiore Hospital for Chronic Diseases.

# POLYOPIA AND MONOCULAR DIPLOPIA OF CEREBRAL ORIGIN

COMMANDER M. B. BENDER, MC(S), U.S.N.R.

Polyopia, or the seeing of multiple images n focusing on one object, is a relatively uncom- ıon condition. This optical illusion is allied ɔ that of monocular diplopia, or the seeing of two images with one eye. Although these symptoms may be found with hysteria, there are many and varied organic conditions which can produce formation of multiple images.[1] Diseases of the ocular media are known to produce monocular diplopia or even polyopia. Here the explanation involves a simple consideration of the physics of light and optics.[2] The same illusion can be reproduced in the normal subject merely by placing an appropriate lens or prism before the intact eye.

Another seemingly peripheral cause of monocular diplopia is strabismus, with resultant reduction in visual acuity. Bielschowsky[3] described the case of a man who had convergent strabismus and amblyopia in the left eye. The patient lost his normal, right eye, and after this he suffered from troublesome monocular diplopia. Vision in the remaining eye, which originally was reduced to ability to count fingers at 6 meters, improved when he learned to fix with the congenital macula. During this learning period, the patient used not only the true macula but the false macula produced by the ocular strabismus. Thus these two foveal points were stimulated at different times. Consequently in the foveal "area" there developed two "space values" for each retinal point, and this resulted in persistent diplopia.

Cass[4] found that 33 of 70 patients with squint had monocular diplopia under certain conditions. He elicited the diplopia by stimulating the abnormal, or "eccentric," fixation point (false macula) in the squinted eye, which corresponded to the true macula of the normal eye. He explained the monocular diplopia on a psychologic basis and stated that it was caused by bringing into consciousness simultaneously the retinal "space values" of the congenital (true) macula and of the acquired (false) macula.[5] In his discussion, Cass considered the relationship between the eye and the body image to objects in space. To a certain extent, the development of one's orientation of objects in space with regard to one's own body during the act of vision depends on the combination of sight and other sense modalities.

Monocular diplopia has also been noted in patients who have involuntary tonic deviation of the eyes due to lesions of the cerebellum or disease of the vestibular mechanisms and in persons who have difficulty in convergence.[6] In some cases it may be present when the eyes are deviated in the extreme lateral position (either with or without nystagmus in such position). However, the monocular diplopia in these conditions is transitory and depends largely on the position of the eyes. Uniocular diplopia and binocular triplopia have been found in patients with lesions of the pituitary implicating the optic chiasm. In these patients a large vertical scotoma situated in the midportion of the field of vision of one eye may be found.[7]

Lesions of the occipital lobe or of the central visual pathways may also produce monocular diplopia and polyopia. The etiologic factors are varied. Encephalitis, multiple sclerosis, trauma

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

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth in this article are those of the writer and are not to be construed as official or reflecting the policies of the Navy Department.

1. Pincus, M. H.: Monocular Diplopia, Am. J. Ophth. **24**:503-506, 1941.

2. Verhoeff, F. H.: The Cause of a Special Form of Monocular Diplopia, Arch. Ophth. **29**:565-572, 1900.

3. Bielschowsky, A.: Ueber monokuläre Diplopie ohne physikalische Grundlage nebst Bemerkungen über das Sehen Schielender, Arch. f. Ophth. **44**:143, 1898.

4. Cass, E. E.: Monocular Diplopia Occurring in Cases of Squint, Brit. J. Ophth. **25**:565-577, 1941.

5. Each retinal point has a definite orientation in space with regard to the macula. In turn, each retinal point has a functional "space value" corresponding to the "space value" of a retinal point in the other eye.

6. (*a*) Klein, R., and Stein, R.: Ueber einen Tumor des Kleinhirns mit anfallsweise auftretendem Tonusverlust und monokulärer Diplopie bzw. binokulärer Triplopie, Arch. f. Psychiat. **102**:478-492, 1934. (*b*) Gerstmann, J., and Kestenbaum, A.: Monokuläres Doppeltsehen bei cerebralen Erkrankungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **128**:42-56, 1930.

7. Author's personal observation in 3 cases.

and tumor are some of the diseases which have been mentioned.[6b]

Hoff and Pötzl[8] reported the case of a 49 year old man who had monocular diplopia and, later, polyopia as a result of tumor in the right occipital lobe. This they explained by a stretching of the occipital cortex in its polar extremity. They proposed the theory that polyopia is the result of concomitant tendencies of two visual functions interfering with each other; the attempt to fixate the object is hampered by forced conjugate deviations of the eyes. Fixation is faulty, owing to the involvement of the occipital pole, and the impulse to deviate is due to irritation of the occipital cortex.

Goldstein,[9] in an interesting paper, described 3 cases of monocular diplopia. Two of the patients had disturbances in the field of vision, while the third patient, with a lesion of the posterior fossa, had abnormal tonic pull in the muscles of the eyes. The author explained the monocular diplopia in the first 2 cases on the following basis: In the attempt to overcome a poor visual performance, the main visual image is displaced to an area where the threshold is normally better, as toward a new fovea. Sometimes the patient sees only the displaced image, but at other times he experiences the first stimulus in addition, so that he sees double. This explanation is somewhat similar to interpretations offered by Bielschowsky[3] and Cass.[4] As for monocular diplopia, in his third case, in which apparently there were no changes in the visual fields, Goldstein argued that the patient, in his effort to overcome the abnormal tonic pulling of the eyes, may maintain fixation on an object only with consequent diplopia. Goldstein further stated that these reactions represent the organism's best possible performance under abnormal conditions. Rather than suffer from blurred vision, the patient manages to see a clear image even though it appears double; diplopia is the "price" the organism has to pay in order to improve the bad vision caused by faulty fixation.

The diplopia in either case is accomplished by a "diffusion" of the visual image after it reaches the cortex. This abnormal "diffusion" of an excitation leads to a spreading of the image perceived, involving areas in the visual cortex which have different "space values." At this point in the process of "diffusion" a new image forms about a new "spatial value," while the old one persists, thus producing two images differing in clarity and intensity. The more foci are involved by the diffusion, the more images are perceived, thus leading to polyopia.

This interpretation seems plausible, but the part of his theory which is difficult to accept is the notion of "diffusion." Although Goldstein referred to some of his older work, there is insufficient proof that "diffusion" of an excitation in the cortex is a principle which is generally recognized in physiology or psychology, unless by diffusion he means the phenomenon of irradiation. Apparently, Goldstein used the term "diffusion" in a pathologic sense, as a disturbance in "figure-ground" formation.[10]

"Diffusion" thus appears to be an inferential concept. On the other hand, observations on patients with a pseudofovea[11] confirm the contention of Goldstein and other earlier investigators that new cortical space values may emerge in such cases and may at times create conflict in the patient's organization of visual space. The question then raised is: How and in what circumstances are such new space values activated? This may be partly answered by studying the following cases.

## REPORT OF CASES

CASE 1.—D. G. H., a 20 year old Marine, corporal, was wounded in the back of his head by shrapnel. This rendered him unconscious. When he recovered, shortly thereafter, he found he was totally blind and had a humming noise in the ears. He remembered he heard voices, which seemed to be distant. Within a few hours after he was injured a craniotomy was performed, and a large gaping wound was noted in the occipital bone. A piece of the calvaria 1½ inches (3.7 cm.) in diameter was found to be depressed below the inner table on the left side. On elevation of the fragment of bone, the dura was observed to be torn, and the underlying brain tissue appeared to be "pulped." After appropriate surgical manipulation, the wound was closed, and the patient was evacuated from the combat area. Aboard ship,

8. Hoff, H., and Pötzl, O.: Zur diagnostischen Bedeutung der Polyopie bei Tumoren des Occipitalhirnes, Ztschr. f. d. ges. Neurol. u. Psychiat. **152**:433-450, 1935.

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.

10. The term "figure" and "ground" in the usage of Gestalt psychology denotes a general principle of organization of visual perception. During the act of perception the "figure" is represented in the cortex by an area of highest excitation, while the surrounding area of excitation represents the "ground" of the percept. Goldstein assumed that under pathologic conditions the distinctness of the "figure" may be decreased by an abnormal spread or diffusion of excitation on the "ground."

11. Kanzer, M., and Bender, M. B.: Spatial Disorientation with Homonymous Defects of the Visual Field, Arch. Ophth. **21**:439-446 (March) 1939. Bender, M. B., and Kanzer, M. G.: Dynamics of Homonymous Hemianopia and Preservation of Central Vision, Brain **62**:404-421, 1939. Bender, M. B., and Furlow, L. T.: Visual Disturbances Produced by Bilateral Lesions of the Occipital Lobes with Central Scotomas, Arch. Neurol. & Psychiat. **53**:165-170 (March) 1945.

and on the second postoperative day, convulsions were noted. These seizures, jacksonian in character, were present periodically for over eight days.

For a short while he had signs of increased intracranial pressure, but despite this he improved. On the fifteenth postoperative day, a cursory examination disclosed that, although he had recovered his vision, homonymous hemianopsia remained. There were no other notations as to his visual symptoms. However, when the patient was interviewed, two months after the injury, the following history was obtained:

For the first three or four days he was completely blind. Then perception of light returned, and everything before him appeared gray and blurred, as if he were looking through a fog. He appreciated motion but could not recognize form. He was not aware of objects, nor could he detect them unless they were in motion.

*Polyopia and Diplopia.*—On or about the seventh or eighth day after the injury, he began to recognize the form of objects, but these appeared to be multiple. Everything around him seemed to be quadruple, no matter in what direction he looked. The four images were arranged in two parallel pairs, one above the other. Everything seemed to be indistinct, and he was unable to diffentiate the true from the false images. They all appeared to be of the same size. At a near point the illusionary figures seemed to overlap, and as the object he was regarding moved away from him the images became rapidly smaller. He also found that on turning his head to one side all the images tended to move in the opposite direction and that when he laid his head on the side they tilted but kept in multiples of four, with one pair above the other. This multiple vision made him feel nauseous and dizzy, and, to avoid the uncomfortable sensations, he kept his eyes closed most of the time. He was unable to adjust to this quadruple vision, which he had for five days. After this he noticed that his sight was somewhat better and that the vision became double when he looked in certain directions, as on turning his head to the right.[12] At that time he could differentiate the true from the false image. The diplopia was only in the horizontal meridian, whereas the quadruplopia was along the vertical and horizontal meridians.

He continued to improve. On about the seventeenth day after the injury, the quadruple vision disappeared, and he had only diplopia. Subsequently, he noted that if he turned to the right or viewed objects with his left upper field of vision, the image appeared to be clear and single. All around this "clear spot" he said objects were "blurred and double." Thus, if he sighted a string suspended in the left upper field of vision, part of the string was clear and single, while the rest was blurred and double. On about the twenty-seventh day after the injury, his vision was much improved, and he no longer had the illusion of multiple images. There were no hallucinations.

*Disturbance in Space Perception.*—As soon as he was able to recognize the form and shape of objects, he found he had difficulty in reaching for food on the tray or for toilet articles not only because of the polyopia but because he overshot his mark. On several occasions he thought he was speaking to some one far away, but actually the person was nearby.

12. Ocular muscle paresis could not be excluded, since the patient did not know whether the diplopia was binocular or monocular. He did not test his vision with one eye covered.

*Perception of Time.*—Time seemed to pass very quickly. What appeared to him to be a few days turned out to be a few weeks. He felt that objects tended to move away from him at a rate much faster than the ordinary. Thus, he found that as the nurse walked away from the bed, she reached a distant point in a much shorter period than he expected.

*Perception of Color.*—The ability to appreciate color did not return until about twelve days after he began to see light. During this period objects appeared gray and generally indistinct.

*Other Temporary Symptoms.*—Besides the visual disturbance, he had slight difficulties in calculation, spelling, reading and writing and showed other fragments of aphasia. These symptoms were present only to a minimal extent and disappeared completely four months after the injury.

*Past History.*—The past medical and social histories were noncontributory. He had completed but two years of high school. He had always been mild mannered, calm and phlegmatic. He denied having a preenlistment anamnesis of neurotic traits and reactions.

*Physical and Neurologic Examination.*—His condition was essentially normal except for the healed wound over the occiput, a hearing defect on the left side and the visual disturbances, to be described later. A roentgenogram of the skull revealed a circular defect 4.5 by 5 cm. in the left occipital bone, with four radiating fracture lines (fig. 1).

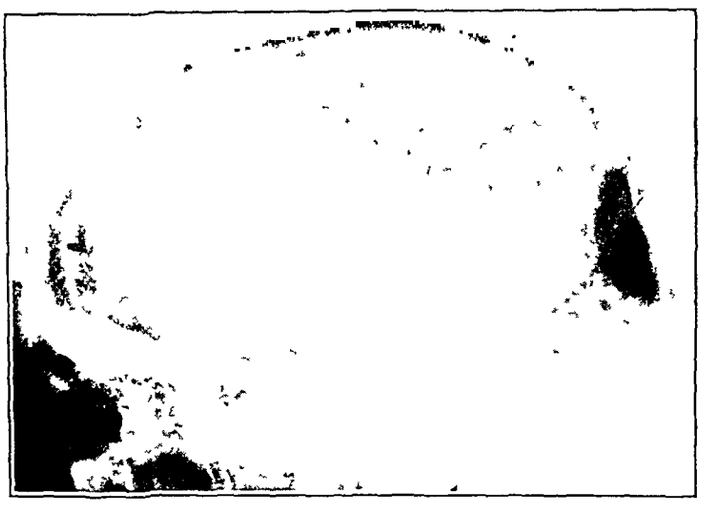


Fig. 1 (case 1).—Roentgenogram of the skull, illustrating the defect in the left occipital bone produced by the shrapnel wound and operation for removal of fragments of bone.

Special personality and psychologic tests failed to disclose significant neurotic trends.

The retina, optic nerve and macula of each eye appeared normal. The movements of the ocular globes were full, and there was no evidence of latent paresis with the red glass test. Ability to fuse images and stereoscopic vision were normal when tested six months after the injury. There was no nystagmus. The pupils were equal and reacted well to light and in convergence. Opticomotor nystagmus was found when the revolving striped drum, held vertically before the eyes, was rotated to the left or to the right. When the drum was held horizontally and rotated downward, there was normal nystagmus, but not when it was rotated upward. The dark adaptation time was seven and one-half minutes on the Feldman adaptometer. (The highest normal value on this instrument is five minutes.)

Perimetric examination for motion disclosed defects in all but the left homonymous superior quadrants of the fields of vision (fig. 2*A*). The defects appeared to be incongruent. The exact border of the area for complete loss of perception for motion could not be plotted with any degree of certainty, for within the zone of indistinct vision (stippled area) there were islands of complete blindness. However, these scotomas were inconstant and on several occasions tended to assume a circular shape, an incomplete "ring scotoma." On the tangent screen, the scotomatous changes about the fixation point were more clearly demonstrated (fig. 2*B*).[13]

*Tachistoscopic Examination.*[14]—With one-tenth second exposures, these tests disclosed marked weakness in perception, particularly in the defective visual quadrants. At this speed the patient also showed difficulty in recognition of color. Reduction in the speed of exposure did not materially improve his perceptive abilities. Reexamination with one-tenth second exposures, repeated

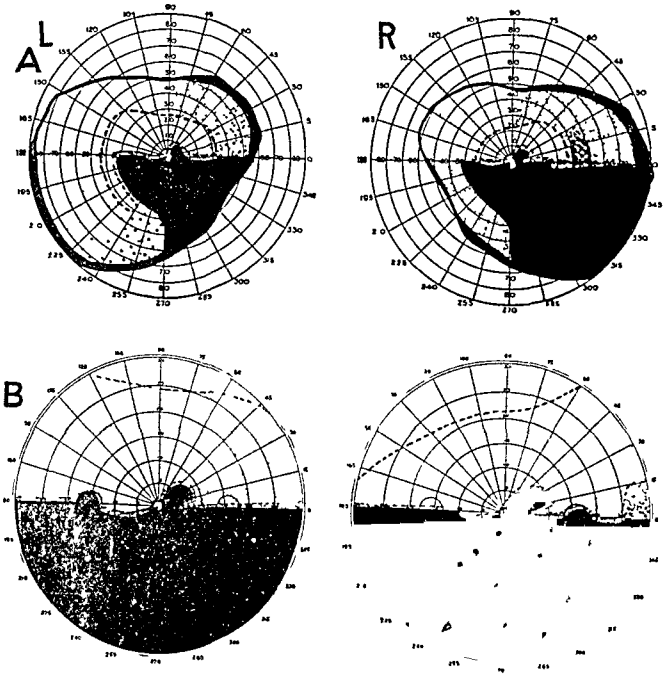



Fig. 2 (case 1).—Fields of vision as plotted on the perimeter (*A*) and the tangent screen (*B*) with a test object 5 mm. in diameter, an illumination of 7 foot candles and a distance from the fixation point of 33 cm. Solid black areas represent loss of perception of motion, and stippled areas, loss of recognition of form and color for objects of 5 mm. diameter. In this figure, and in figure 5, the degree of impairment is indicated by the size and density of the dots. The area within the line of dashes indicates preservation of color. The fields are incongruent. In the temporal field of the right eye there appeared to be a transient ringlike zone of defective vision.

five months after the injury, revealed improvement in perception of form and color and in interpretation of exposed drawings of familiar objects. With short exposures the patient was able to detect figures in areas which seemed to be deficient for recognition of form, and even motion, when tested on the tangent screen or with one or two second exposures on the tachistoscopic screen.

*Visual After-Image.*—The after-image the patient had was usually incomplete, inasmuch as he could see only the left upper portion of an object on which he was fixing. Thus, after fixing for thirty seconds on the star in the right lower corner of the American flag painted in green, black and yellow, the negative after-image he saw on a white background was in complementary colors. However, he saw only parts of the flag—the blue field with white stars and one or two red and white stripes below the field. The rest of the flag was not visualized in the after-image. The fixation was made at a distance of 10 inches (25 cm.). When he fixated on the flag at a greater distance, such as 20 inches (50 cm.), the after-image was more complete. He then visualized all but the right lower quadrant. Apparently, he had an after-image of a part of the field of which he was not aware with the ordinary tests, such as the tangent screen or the perimetric test. The same after-imagery responses were obtained when he closed his eyes after thirty seconds of fixation on the star. The after-image obtained in this manner appeared to be much smaller and to be more intensely colored on a black background. Again, the area of the after-image was more extensive than that which he saw in the plotted visual fields.

When he fixated on a light (100 watt bulb behind a convex lens) 3 inches (7.6 cm.) from his eyes for five seconds and then closed his eyes, the after-images he saw appeared within seven seconds and continued with changing colors, from yellow to blue to green to red, for two minutes thereafter. The results obtained were the same in each eye. Evidently, in this test, he showed no deviation from the normal except that on several occasions the shape of the image varied.

*Fluctuation, Obscuration and Extinction of the Visual Images.*—When the patient fixated on the flag, he claimed that at first it seemed as though he saw the entire flag; but when he concentrated on the star, the part of the flag on his right side seemed to have "blacked out," and the rest of the area around the fixation point tended to become gray and to fluctuate in distinctness. When he was asked to fix on a dot about which were drawn four vertical lines, one line being situated in each of the four quadrants about 1.5 cm. from the fixation point, it was noticed that within two to three seconds the line in the right upper quadrant disappeared; the line in the left lower corner (area of defective vision) waxed and waned at a fluctuating rate, the image being present for seven or eight seconds and absent for one or two seconds. These phenomena have been previously described in patients with lesions in the visual pathways.[15]

When he fixated on a central point, it was noticed that he could immediately recognize a large object, such as a pencil, in the right upper quadrant 10 to 15 degrees from the fixation point. However, within five seconds the image of the pencil began to wax and wane, and several times he could not perceive it at all, the image becoming totally extinct. This visual fluctuation, obscuration and transient extinction were not evident in the left superior quadrants of vision. There the object regarded showed only slight fluctuation. On looking

13. Examination was performed under 7 foot candles of illumination at a distance of 35 cm., and a 5 mm. test object was used. Visual acuity was 20/20 in each eye.

14. The examination was performed in a dark room with images flashed on a screen, on which the patient fixated on a central point from a distance of 5 feet (152 cm.),

15. Bender, M. B., and Furlow, L. T.: Phenomenon of Visual Extinction in Homonymous Fields and Psychological Principles Involved, Arch. Neurol. & Psychiat. **53**:29-33 (Jan.) 1945.

in a mirror he usually saw his face; but when he fixated at the bridge of his nose, everything below the nose and to the right seemed to be gone and the space was gray. The observation made here conformed to the results with the tachistoscope, for during a rapid exposure the patient seemed to see objects in apparently defective areas about the central field. He showed no difficulty in recognizing hues and tones of color. There was no sign of defective visual memory and no apparent spatial disorientation at these examinations. He also denied ever having had visual hallucinations.

Examinations on the perimeter and the tangent screen repeated five months after the injury revealed a slight contraction in the extent of the scotoma originally found in the right upper and left lower quadrants of the field of vision.

*Comment.*—It is interesting to note that as the patient's vision improved the polyopia became less apparent and changed into diplopia. This was particularly noticeable at the time when the patient found that on turning his head and eyes in certain directions, especially to the right, vision was better.[16] Evidently, in order to see better, the patient made use of his mechanisms for ocular fixation.

In this zone of improved vision there was diplopia, whereas the rest of the field seemed to present four images. Thus, there were two types of multiple image formation, expressing two degrees of severity of the same functional disturbance. Moreover at a later date, when the patient had only double vision, he found that by turning his head he localized an area of clear and monocular vision. This was on his left side. Apparently, as soon as visual perception improved, the polyopia disappeared. Unfortunately, the patient did not test his visual abilities with one eye closed; so it cannot be stated whether or not he had monocular diplopia or double vision due to inability to fuse images or to palsy of an ocular muscle. However, since he had polyopia and since the diplopia had a similar localization in the field of vision, it is assumed that the formation of double images was of cerebral origin, and probably monocular.

Significant and important were the fluctuation, obscuration and extinction of the perceived image. This phenomenon is known to produce a disturbance in the mechanism of fixation. Such a disturbance might play a role in the formation of multiple images. Also significant was the fact that in one plane, such as that of the suspended string, the patient had a zone of single and clear vision, with double, blurred vision above this zone.

Another interesting symptom presented by this patient was a spatial disorientation in his remaining field of vision. Such a visual disturbance, which was described by Riddoch[17] and Brain,[18] might be associated with dysfunction in the mechanism of fixation or be caused by a derangement in the space values about a focal visual point.

In the following case, the syndrome of polyopia, spatial disorientation and difficulty in fixation is again noted.

Case 2.—E. McI., a 22 year old Marine, sergeant, was wounded in the right occipital area by enemy machine gunfire. He lost consciousness for a moment or so, and when he recovered he found he was completely blind. Two hours after the injury his sight began to return and he perceived light. Everything appeared blurred. He had a "feeling" that he could not see or look upward. A few hours later, after his head wound was dressed, his sight improved rapidly, but since then his vision had never seemed normal to him.

*Spatial Disorientation.*—For the next five days he was unable to judge distances properly and he could not fixate on an object. In eating he had difficulty in handling the food because he could not gage the distance between the plate and his mouth. He usually fell short of his mark. He also had trouble in estimating the location of an object in space. For instance, on walking through the hatchway of a ship, he was unable properly to judge the position of the door. At this time, he was able to write a letter. He could see the form and shape of an object, although he could not always recognize it.

*Polyopia.*—At first he found he was unable to read or to write because of formation of blurred and multiple images. As he focused on any object he was regarding, the perceived image became blurred. It waxed and waned; and the more he tried to distinguish it the more it tended to become double, and within a few seconds it spread in a horizontal row to his right to become multiple. The multiple images were parallel, close to one another and all of the same size. The row formed a somewhat oblique line, with the images on his right somewhat higher than those on his left. The illusion always developed to his right, and often he felt as if he were turning his eyes or they were being pulled to the right so as to follow the images. This made him feel dizzy, and he had discomfort in his eyes.

The images were generally indistinct and had little color. The farther the object was from him, the dimmer it appeared and the less he could distinguish, even though there were many images. Closing the eyes for a few seconds or just gazing into space without fixation would abolish the illusion. Also, when he turned his eyes back to the left or to the original object, the polyopia would disappear. The polyopic experiences lasted four days, and for the next six days he saw only double when he fixated on an object. At this time the vision and images were not nearly as blurred as when he saw multiple. The diplopia was present directly before him, but the double images "moved to the right"

16. By turning his head and eyes to the right, the patient viewed objects with his left field of vision.

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

18. Brain, R.: Visual Disorientation with Special Reference to Lesions of the Right Cerebral Hemisphere, Brain **64**:244-272, 1941.

in the same manner as in the case of multiple image formation.[19]

*Fluctuation of Visual Image.*—After the diplopia disappeared, he noticed that the waxing and waning of visual images became more apparent. For this reason, he had great difficulty in reading and writing. He found he was forced to close his eyes frequently or to stop reading so as to avoid a "running together" of the printed or written letters and words. With rest his vision became clear, but when he resumed reading the blurring recurred. Associated with the blurring, he felt a sensation of pulling and turning of his eye to the right. These symptoms lasted eight days and disappeared. Except for slight blurring of vision on fixation he was practically asymptomatic, and one month after he was injured he was returned to duty.

He participated in another invasion and returned with his outfit for a rest. Two months after the injury, he noticed that flexion of the neck produced unpleasant vibratory sensations in the lower part of the trunk and hips, radiating to the inner aspect of the thighs. Later, he found that the vibratory sensation rapidly spread into the toes. Subsequently, the upper extremities became affected. He also noted that when he accidentally bent his head while hiking he not only had the vibratory sensation through the body but felt strange in his feet, with a tendency to lose his sense of balance and to stagger. Because of these symptoms he was readmitted to the hospital.[20] Recently, he had found that tapping of the neck or acute flexion would produce a transient sensation of flickering light in both eyes, as if the eyes were opening and closing.

The physical examination revealed an essentially normal condition except for a healed scar over the right occipital region. A roentgenogram of the skull revealed three metallic fragments, each measuring about 0.5 cm. in diameter, in the right occipital area. Underlying this

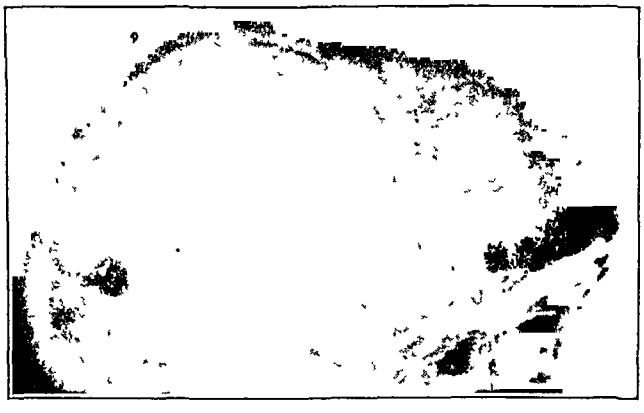


Fig. 3 (case 2).—Roentgenogram of the skull, illustrating the defect produced by a bullet wound in the right occipital region.

scar was a spherical bone defect 1.5 cm. in diameter (fig. 3). An audiometric record disclosed 40 per cent deafness for higher tones in the right ear.

The results of neurologic examination were essentially normal except for a vibratory sensation in the trunk and extremities whenever the neck was flexed acutely. The fundi were normal. The pupils were equal and reacted well to light and in accommodation. The ocular movements were normal. Examination of the visual fields revealed a distinct scotoma in the left homonymous superior quadrant (fig. 4).

*Fluctuation and Obscuration of Vision.*—On fixating at a point with either one or both eyes, the patient complained that objects or figures in his left upper field of vision waned and waxed and that they became obscure and at times disappeared entirely. Thus, a pencil or a watch placed in that area would fluctuate in distinct-

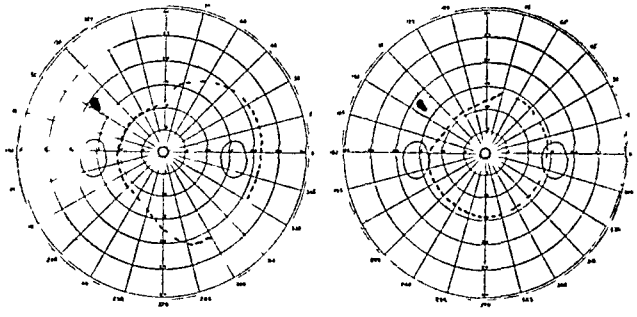


Fig. 4 (case 2).—Visual fields plotted on the tangent screen, illustrating a small scotoma in the left homonymous fields. Objects placed in the left field of vision fluctuated in their appearance, and with double simultaneous stimulations the image became obscure.

ness, become blurred and ultimately disappear from sight. At this time, he felt a pulling in his eyes, and he was unable to maintain his fixation. Also, the introduction of a simultaneous stimulus in his right field of vision would make the image in his left field become dimmer and more indistinct (obscuration phenomena).[15]

*After-Imagery.*—All responses seemed to be normal for form and color with both light and dark backgrounds. Dark adaptation time was five minutes on the Feldman adaptometer, a normal value. Tests for color vision gave normal results.

*Tachistoscopic Test.*—The patient seemed to show a decrease in perception with one-tenth second exposures, with weakness in his left upper field of vision, but this was not pronounced.

*Comment.*—This case is another example of polyopia and diplopia due to a lesion in the occipital lobe. Here, however, the polyopia was along the horizontal meridian, with slight tilting. The illusion developed to the right and seemed to be associated with a forced ocular deviation. As the patient fixated on the object, the image blurred, and he felt as if the eyes pulled to the right. This phenomenon was soon followed by progressive increase in the number of false images to the right. It seemed to him that in order to follow the extra images his eyes "pulled" or turned to the right. What probably happened was that his attempt to fixate on an object produced a fluctuation, later obscuration and sometimes extinction of the image arising from his left field of vision, which was defective.

19. This patient, too, did not test his vision, with one eye closed, so that it could not be established whether he had monocular or binocular diplopia.

20. Similar complaints of dysfunction referable to the spinal cord have been noted in a number of other patients with gunshot wounds of the brain, as far forward as the frontal lobe. In these patients there were no other symptoms or signs of involvement of the spinal cord, nor was there injury anywhere but in the brain.

This resulted in a conflict between the right and the left side of the visuomotor mechanism. The stimuli arising from his right, or normal, field were stronger and reflexly tended to pull his eyes to the right. As the eyes deviated to the right, the regarded stationary object loomed in the left, or defective, field of vision. Of course, when the gaze to the right became extreme and the original stationary object was out of focus, or he no longer saw it, the polyopia disappeared. Also, when he turned his eyes sufficiently to the left so that the object appeared in the right or normal field of vision, the illusion was not present. From these facts it is evident that the multiple images tended to form at the transition between the defective and the normal field of vision and were related to the disturbances produced by attempted fixation, namely, obscuration and extinction of image in his left field of vision. There seemed to be a conflict between fixation and visual performance, as pointed out by Hoff and Pötzl.[8] The transient episode of visual disorientation in space was probably also related to this conflict in function.

Another form of optical illusion of cerebral origin associated with disturbances brought on by fixation is illustrated by the following case.

CASE 3.—J. E. D., a 60 year old veteran of World War I, was admitted to the hospital with a history of progressive weakness and numbness on the left side of the body, especially in the leg, for eight months. He also complained of inability to recognize and of dropping objects with his left hand. He denied having symptoms of visual dysfunction.

*Neurologic Examination.*—Reflex changes and motor and sensory defects were present on the left side of his body. There were mild hemiparesis and a positive Babinski sign. The sensations impaired on that side were pain, temperature, point localization, two point discrimination, position sense of digits and toes in space, stereognosis and graphesthesia. The sensory adaptation time was much reduced on the left side. All these sensations became totally extinct with the method of double simultaneous stimulation.[21]. Thus, although he could partly perceive a painful stimulus when applied to any one part of the left side of his body (distal portions were most affected), this sensation was not present when another stimulus was applied simultaneously to the corresponding part on the right side. This was true not only for pain sensibilities but for other modalities, especially graphesthesia. Even the crude sensation evoked by rubbing became extinct when both sides (hands) were rubbed simultaneously.

*Psychiatric Examination.*—Special psychologic examinations, including the object-sorting test as devised by Goldstein and Scheerer,[22] revealed abnormal rigidity of thinking. Abstract reasoning was very poor. In grouping and sorting objects, even when prodded, he persisted in the same mental set. He arranged materials according to their everyday use. There was resistance to all the examiner's suggestions to shift to different principles of sorting. He had a tendency to be satisfied with a simple pairing of objects, and he insisted on continual manipulation of those objects which he grouped. There was extreme concreteness in his thought processes. In general, he was cooperative and persistent in his efforts. His responses appeared to be reliable and consistent.

He manifested no other signs of intellectual deterioration. His memory was good. Aside from being somewhat facetious and slightly euphoric, there was no gross disturbance of the affect. Orientation and insight were normal, but judgment was somewhat defective.

*Physical Examination.*—He had signs of generalized arteriosclerosis to a degree consistent with his age.[23]

*Ocular Examination.*—The pupils were equal and reacted well to light and in accommodation. The fundi revealed retinal arteriosclerosis and normal optic disks. The ocular movements appeared to be normal and showed no apparent muscular palsy. However, during fixation it was frequently noted that the head was tilted reflexly, or without his awareness, so as to bring the object regarded into his right field of vision. The cornea, lens, other ocular media, retina and macula of each eye were normal. He had mild astigmatism, which could be corrected.

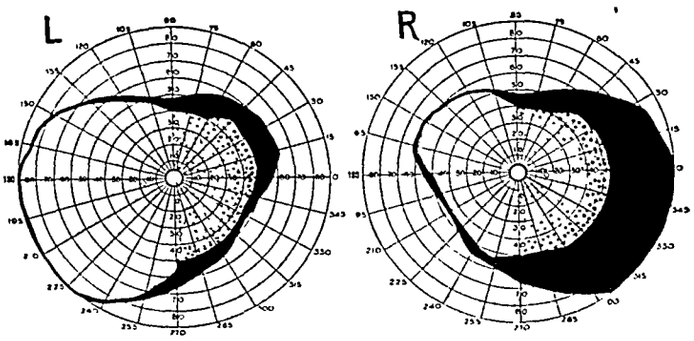



Fig. 5 (case 3).—Visual fields plotted on the perimeter, illustrating concentric form of the left homonymous field defects. With double stimulation, even perception of motion became extinct in the remaining left field of vision.

*Visual Fields and Extinction Phenomena.*—Gross examination of the visual fields disclosed a left homonymous field defect, but this was not absolute (fig. 5). He could perceive motion in the left homonymous fields, but with simultaneous stimulation in the right and left temporal fields of vision, he perceived the image only in the right field; the image in the left field became extinct. The same extinction phenomenon was present on fixation of stationary objects. He had difficulty in differentiating certain hues, especially dark-toned colors.

*Tachistoscopic Examination.*—Exposure of images for one-tenth second under dark-adapted conditions disclosed weakness of perception in his left field of vision. With

21. Bender, M. B.: Extinction and Precipitation of Cutaneous Sensory Phenomena Illustrating Bilateral Functional Relationship of Sensation, Arch. Neurol. & Psychiat. **54**:1-9 (July) 1945.

22. Goldstein, K., and Scheerer, M.: Abstract and Concrete Behavior: An Experimental Study with Special Tests, Psychol. Monogr. **53**:1-151, 1941.

23. The patient offered a diagnostic problem, which to date has not been solved. Although the clinical course was that of a slowly progressive lesion, which seemed to originate in the leg area and involve largely the visual and sensory functions of the right side of the brain, there was no conclusive evidence of the presence of a space-occupying lesion. The pneumoencephalogram and the ventriculogram were considered to be essentially normal.

longer exposures, the images on his left became totally extinct. He showed normal ability to recognize images in his right field of vision when the objects were flashed at a speed of one-tenth second.

*After-Imagery.*—Repeated visual stimulation with strong light in either eye for fifteen or twenty-five second periods produced only a slight visual after-image, such as a "gray smudge," which lasted a few seconds. There were no color changes, as noted with the normal subject, who experiences a series of changes through yellow, blue, green, red, etc., even with as short a stimulus as three seconds. Gazing at the American flag for fifty seconds produced no visual after-image. However, after staring at the flag for fifty-five or sixty seconds, the patient saw an after-image of several brown stripes in his right upper field of vision. Besides these two vague responses, no visual after-images could be elicited with strong or weak, short or prolonged visual stimulations.[24] Neither positive nor negative after-images could be evoked from exposures to black or white objects under dark-adapted or light-adapted conditions. The fluctuation normally found on gazing at the Schröder staircase could not be elicited in this patient. However, he reported a fluctuating rhythm between green and red when a green lens was before his left eye and a red lens before his right eye.

*Visual Retention.*—The patient was confronted with a set of cards showing simple geometric figures. Each was exposed for ten seconds, and he was asked to draw what he saw.[25] Of the seven cards shown to him, he did well on all except that he tended to omit objects exposed in his left field of vision. Thus, when shown a small square, a large circle and a large triangle, he invariably drew the circle and triangle and omitted the square, but when the card was reversed, so that the square was on his right, he drew all the three objects presented or omitted the figures on his left side.

*Monocular Diplopia, Polyopia and Other Optic Illusions.*—I. The Illusion on Fixation of a Single Line: When the patient was shown lines or figures and asked to draw what he saw, he did so rather promptly, and all of his recorded images were correct and single. However, after he focused on a line for ten or more seconds, there appeared a second line parallel to the one he was regarding, and he saw two lines, one dark and one light (fig. 6 *D-G*). The latency varied between seven and thirty-five seconds. He saw two images with either one or both eyes and irrespective of the meridian in which the fixated line was situated. During fixation he invariably tilted and turned his head so as to bring the observed line into his right field of vision. Movements of the head produced movement of the light line. He felt that the heavy line was more or less stationary. It was difficult for him to decide in which direction the line was moving relative to his head, but in general it seemed to him that the movements were to the opposite side. The monocular or binocular diplopia appeared only when he regarded thin lines. A thick line seldom produced the illusion of double image, although it tended to widen and on one occasion split in two. Actually, he never saw the splitting or the movement by which the second image appeared. On looking at a fountain pen for fifteen seconds, he noticed that it broadened and appeared distorted. The thinner the line, the clearer was the diplopia. Usually the images were 1/16 or 1/8 and 1/4 inch (1.6 or 3.2 and 6.4 mm.) apart when the eye was at

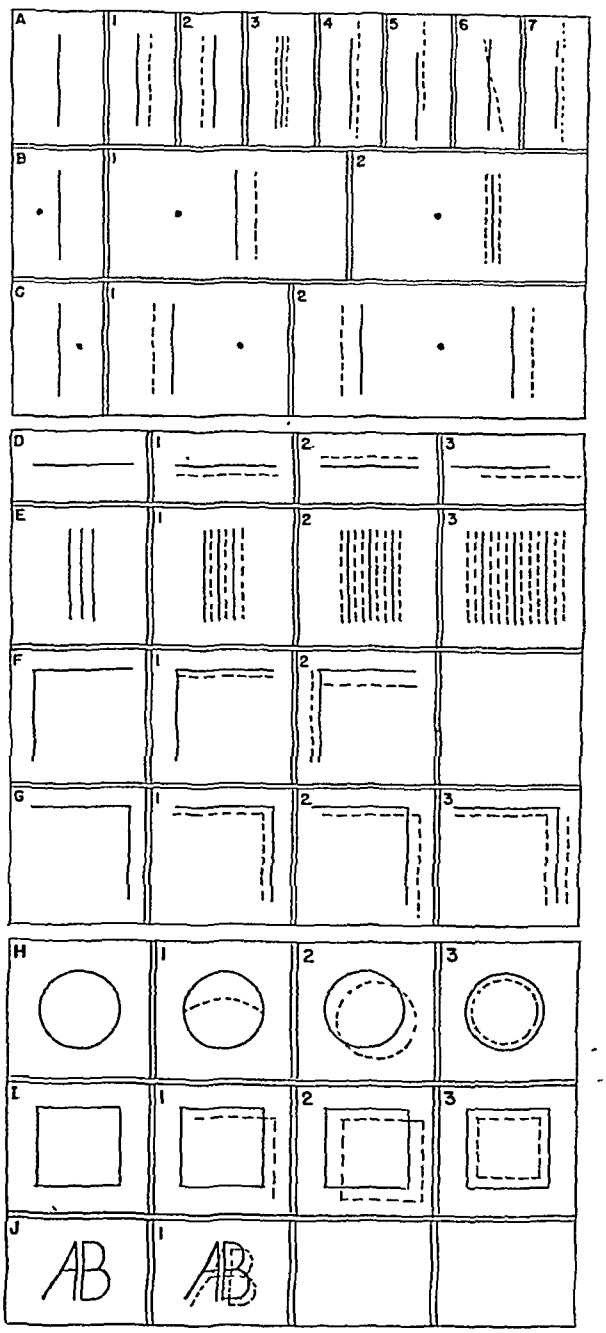



Fig. 6 (case 3).—Chart illustrating what the patient saw when presented with an object before one eye. In the first column is the drawing of the figure which was shown to him; in the columns to the right are the drawings of what he saw. The solid line represents the heavy image, while the line of dashes indicates the light image. For interpretation of these drawings, see the text.

24. Two months later this patient showed improvement. The monocular diplopia became less pronounced, and his ability to see visual after-images partially returned. On reexamination, he reported, after fifty seconds' exposure, a rectangular after-image of the American flag (drawn in complementary colors). Again, he saw dark brown stripes and part of the left corner field. He was characteristically unable to specify the color of spaces between these dark brown stripes, but after some reflection he concluded that they must have been "light gray." The seemingly pedantic nature of the patient's color descriptions is evidently related to his concrete mental approach.[22]

25. Benton, A. L.: A Visual Retention Test for Clinical Use, Arch. Neurol. & Psychiat. **54**:212 (Sept.) 1945.

a distance of 10 to 12 inches (25 to 30 cm.) from the fixation point. Occasionally, he found the lighter image to be longer than the dark one. In attempts to differentiate the true from the false image, it was found that the dark, as well as the light, line was displaced from the original. The following experiments reveal some of the conditions under which the monocular diplopia could be elicited.

1. Monocular diplopia was found with either or both eyes when he was fixating on a line.

The patient was asked to fix on a thin vertical line. After the usual latency a double image appeared. When asked to indicate each of the lines he perceived, he pointed to two lines, one situated to the left and one to the right of the originally fixated line (fig. 6 *A 1* or *2*). He was not aware of the original line.

2. The double image appeared to be displaced.

When asked to fix at a point situated ¼ inch to the left of a vertical line, he saw after some delay two lines. When asked to put a pencil mark on each line, he pointed about ¾ to 1 inch (1.9 to 2.5 cm.) to the right of the original line, which, again, he did not see (fig. 6 *B 1*). At this moment, when asked to show the position of the dot, he at first localized it slightly to the right of the original, but then he corrected himself. He also had difficulty in finding the original vertical line, and when he did so the two illusionary lines disappeared.

3. Double images appeared to each side of a fixated point.

When he was asked to fix on a dot situated ¼ inch to the right of a vertical line, the chin turned slightly to the left while the head and eyes rotated slightly to the right. As he executed these movements, and after a latency of three seconds, he saw two lines on his left (fig. 6 *C 1*) and in three more seconds another two lines, so that he saw a total of four lines, one pair about 1 inch to the left and another pair 1 inch to the right of the fixated dot (fig. 6 *C 2*).

4. The diplopia appeared even while the original image was moved from one side to the other of a fixated point.

The patient was asked to fix on the point of a thin stick which was placed over a piece of paper on which there was a vertical line. As he focused on the point, the paper with the line was moved laterally, and within five to ten seconds the vertical line became double. The image remained double even when the line was moved to the left or to the right, or first from right to left across the fixation point. The diplopia persisted even while the paper with the vertical line was being rotated 90 to 180 degrees.

5. The patient had formation of double images when the fixation point and the vertical line were separated by a visual angle of 2 degrees.

The patient was asked to maintain his gaze on a moving point while the exposed line remained still. Again, the image appeared double after the usual latency. In this experiment, the original image was kept stationary while the fixation point was moved to the right or to the left of the exposed line. No difference in the diplopia was elicited by this method when the object was exposed to the right and to the left of the fixation point, as in experiment 4.

6. Monocular diplopia was present for lines in the horizontal meridian.

Experiments 4 and 5 were repeated with the object a horizontal line and the fixation point changed absolutely or relatively along the vertical meridian. The same results were obtained (fig. 6 *D*). The diplopia was found to be present over a radius of ¾ inch from the fixation point, or a visual angle of 2 degrees.

7. The double or multiple images were present within a definite range along the visual axis.

Thus, the exposed object appeared (*a*) blurred when situated less than 15 cm., (*b*) clear but double when situated between 15 and 63 cm. and (*c*) clear and single when situated more than 63 cm., from the eye. The diplopia and polyopia were most pronounced when the exposed line was set between 25 and 40 cm. from the cornea.

8. The partial or complete covering of the exposed object produced a concomitant disappearance of the illusionary images.

Experiment 2 was repeated. When the image appeared to be double and displaced about ¾ inch lateral to the position of the regarded object, a piece of paper was placed on the original line. This immediately caused disappearance of the induced double images. As soon as the paper was removed and the line was reexposed, the patient again saw the two lines. Covering only a part of the line resulted in the eclipse of that part of the double image.

These observations seem to indicate that the images the patient had of a fixated line were false, despite the fact that one of them was dark and the other light. One may claim that the dark line is a displaced true image. This, however, is invalidated by the observation made in experiment 3. There the patient saw a dark and a light line to the left and a similar pair to the right, of a fixated point. Thus, in a field where only one line was exposed ¼ inch to the left of a focused dot, the patient saw two dark and two light lines (fig. 6 *C 2*).

II. Polyopia and the Illusion Found on Fixation of More than One Line: When the patient looked at two or three parallel lines, he saw six, at times nine and once twelve, lines (fig. 6 *E 1* to *3*). Thus, the patient had not only monocular diplopia but polyopia (see also fig. 6 *A 3* and *B 2*). The polyopic images were parallel, and most of them were lighter than the original. When asked to count the heavy lines, he pointed out three of them, but at times he thought he saw more. Because of the great number of lines, he became confused when he attempted to count them. He found it difficult to determine on which side the lighter images appeared. Usually, however, he located them to the right. Thus, while studying the position of the six images, he discovered three more on slight turn of his head to the left, and with another slight turn he saw three more, forming a total of twelve (fig. 6 *E 3*).

Focusing on lines drawn in two planes was also accompanied by monocular or binocular diplopia, after a latency of eight to fifteen seconds. The entire image appeared double. However, if the greater part of the exposed figure was in the patient's right field of vision, he saw double only for the part exposed in his right field (fig. 6 *F*). This was inconstant and depended on the point of fixation.

III. Illusions Produced by Curved Lines, Geometric Figures and Other Mixed Lines: When asked to draw what he saw on fixating on a circle, he gave three types of responses: a circle, with a lighter arc drawn within it; two circles, one linked above with the other, and or a circle within a circle (fig. 6 *H*). On looking at a square, he saw double after a given latency (fig. 6 *I*). At times the double image was incomplete (fig. 6 *I 1* and *H 6*). When he was asked to draw the letters *A* and *B* after he had fixated on them, he drew a double image of each (fig. 6 *I*).

IV. Other Illusions: On occasions he noted a discontinuity in the dark and light lines of the double image, usually in the upper part of the field of vision. The patient volunteered that the lines, circles or geomet-

ric figures had "gaps" in their upper portions (fig. 6 *A 7*).

In general, most of the illusionary figures were parallel, but on one or two occasions there was a tilt of one of the two images seen on fixating on a single straight line (fig. 6 *A 6*). On several occasions, it was found that one vertical line was slightly lower than the other (fig. 6 *A 5*) or one horizontal line was farther to the left or to the right than the other (fig. 6 *D 3*) or one was somewhat longer than the other (fig. 6 *A 4*).

As stated before, the latency varied. However, once the patient had monocular diplopia or polyopia, he was able to see as double all other objects submitted to him within a very short latent period of one to three seconds. When the eyes were rested, by closing the lids for more than fifteen seconds, and the tests were then resumed, the latency for the monocular diplopia was again prolonged to ten or twenty-five seconds. If the rest was less than ten seconds, the latency remained short, i. e., one to three seconds. The patient had no difficulty in reading as long as he did not stop to look at one spot for any length of time.

*Comment.*—This case demonstrated several interesting phenomena: (1) extinction of visual, as well as of cutaneous, sensations on the left when the right and the left side were stimulated simultaneously; (2) defective visual after-imagery; (3) impairment of the mechanism of fixation and (4) monocular diplopia, polyopia and other optic illusions on attempted fixation.

It is significant (*a*) that the multiple images in this case did not occur unless the objects studied were represented by thin lines, (*b*) that they did not appear unless the object was fixated over a latent period, which sometimes lasted thirty-five seconds, and (*c*) that the illusion was present only in a given zone of the projected field of vision. Also important were the association of the diplopia with observable deviation of the eyes and the displacement of all the images. This displacement took place usually to the right, but in many instances also to the left. However, the change in the position of the images occurred even without deviation of the eyes (experiments 4 and 5).

It was not always related to the position of the eyes; thus, the patient saw double while the exposed object was rotated slowly through 180 degrees. If it was rotated rapidly, the diplopia disappeared. Still another important observation was that the illusion appeared only within a certain range—within 2 to 3 degrees of the fixation point and between 15 and 65 cm. from the cornea. Beyond these limits there was no monocular diplopia or polyopia. Evidently, the illusions depended on fixation and seemed to be related to the conflict between the right and the left field of vision.

CASE 4.—J. P. F., a 20 year old seaman, second class, was admitted to the hospital with a temperature of 106 F. He had a maculopapulomorbilliform eruption over the face and trunk, Koplik's spots, pharyngitis and conjunctivitis. The diagnosis was measles. For the firs six days the temperature ranged from 101 to 105 F. He was treated with penicillin and apparently improved. Fifteen days after the onset of the illness, his temperature again rose to 102 F., and he became restless and suffered from insomnia. He had diarrhea, urinary retention and defective vision, and there developed typical signs of paralysis agitans. There were bradykinesia; forward bending of the trunk; abduction of the arms with loss of associated arm and finger movements; pill-rolling tremor of the fingers, especially on the right; increased muscular tone; fixed and greasy facies, and infrequent blinking. There was a congenital convergent squint in the left eye. In addition, he had many visual disturbances, which will be described in detail later. On psychiatric examination, he was found to be euphoric, facetious and impulsive. At times he showed involuntary laughter. Memory was defective, and calculation was poor. There was severe insomnia, and one night he had visual hallucinations. He also showed compulsive and obsessive phenomena. He was unable to adjust to the temperature of the room. He often complained that it was cold when actually the temperature was above 80 F., and vice versa. For several days he had urinary retention, and once he was incontinent. Except for leukocytosis, all laboratory studies, including those of the spinal fluid, revealed nothing abnormal.

By the fifth week of his illness he was much improved. The mental symptoms had subsided; the tremor and other signs of paralysis agitans were minimal. The arm swing returned, and the facies became more expressive. However, he still complained of defective vision (that objects were obscure) and of inability to read quickly or to see individual units. He had illusions of seeing groups of objects which seemed to be displaced in space. Some of these visual symptoms persisted for several weeks. The plotted visual fields failed to disclose any gross scotomas or contraction. Visual acuity was 10/40 in the right eye and 10/50 in the left eye. During his convalescent period, he was observed frequently, and numerous studies revealed pronounced defects in the visual perceptive mechanisms.

In the first few weeks of his illness, he showed marked defects in perception, as tested with the tachistoscope. Even with one second exposures, he was unable to detect simple objects, letters, geometric figures or colors. But with longer exposures he could identify each of the objects presented.

His drawings were extremely poor. They showed marked disproportion of the figures and ground and omission of essential lines, contours and shadows. He knew a hexagon had six sides, but he drew only five. On drawing a checkerboard, he failed to differentiate black and white squares. Visual retention was defective, inasmuch as he omitted details.[25] Dark adaptation time was nine and one-half minutes on the Feldman adaptometer.

Visual after-imagery had disappeared almost completely.[26] The only visual after-image which could be elicited in this patient was that induced by shining a strong light in either eye. After a five second stimulus, he saw in the dark, or with his eyes closed, a small round white light, which persisted for over eight minutes without changing its color.[27]

26. The patient stated that prior to his illness he was able to see negative after-images with black, white and various color stimuli.

27. In the normal subject such a stimulus produces a visual after-image of a white-yellow light, which changes to blue, to green, to red, and ultimately to black and tends to disappear entirely within two to three minutes.

He complained of inability to read as quickly as he could prior to his illness. He had to follow the print slowly or he would skip words. He could not recognize simple words when they were inverted or turned 90 degrees to the horizontal. When he looked at a picture magazine, he could not appreciate what he saw at a glance. It was necessary to study individual parts "to see the picture or to get its meaning."

About this time, special tests revealed defectiveness in visual organization which approached genuine visual agnosia. On attempting the "performance scales" of the Bellevue-Wechsler intelligence test, the patient was unable to visualize the "hand" which had to be assembled from seven irregularly shaped pieces of wood. After ending his performance with an absurd configuration, he indicated to the examiner that he was aware of his failure.

Color vision at this time appeared to be normal, but he had great difficulty in recognizing the figures exposed in color tests, especially on the tachistoscope.

During the sixth week of his illness, he noticed small yellow "spots and bands" whenever he regarded an object or print. These spots moved with his eyes and were present even when his eyes were closed.

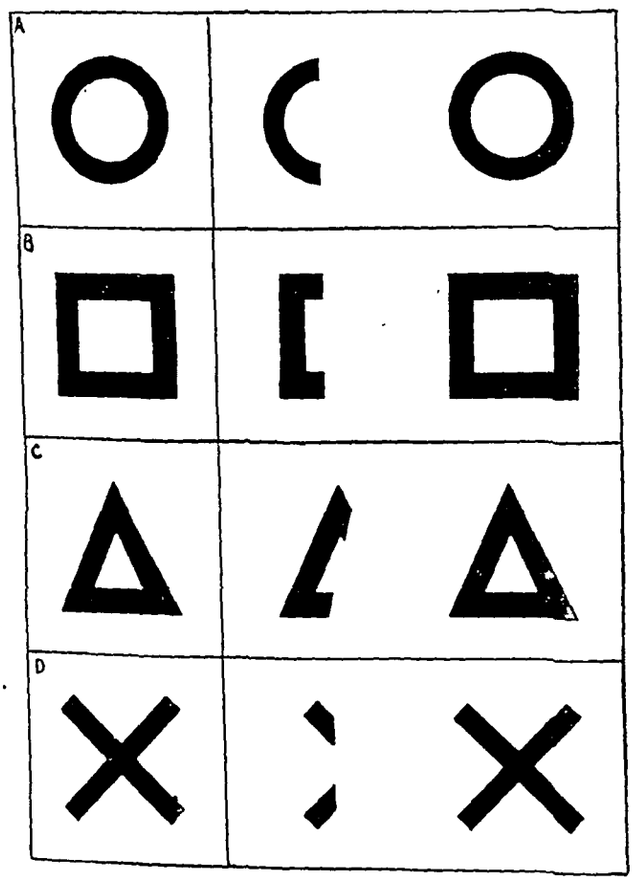



Fig. 7 (case 4).—Chart illustrating what the patient saw when he looked at simple geometric figures. In the first column is the figure shown to the patient, and in columns to the right are the drawings of what the patient perceived.

During the seventh week of his illness, some of his ability to see after-images had returned. When the American flag in complementary colors of some other colored object was exposed, he saw a small gray after-image of the exposed object. He saw the background or outline but not the figure. The following week he noticed the figure, but it was gray. Thus, he saw gray and white stripes instead of the red and white stripes of the American flag. Negative after-imagery in complementary colors did not return until several weeks later, and then it could be elicited only after prolonged stimulation. The patient could see negative after-images of thick black lines. When he discovered that he had regained part of his power of visual after-imagery, he rejoiced and repeatedly tested himself by exposing his eyes to all sorts of black lines and figures. However, after a few days of such experimenting, the patient began to see double. He complained that on looking at black objects he saw another partial image to the left of the original. This was present when he used both eyes or when he closed the left eye. At first he

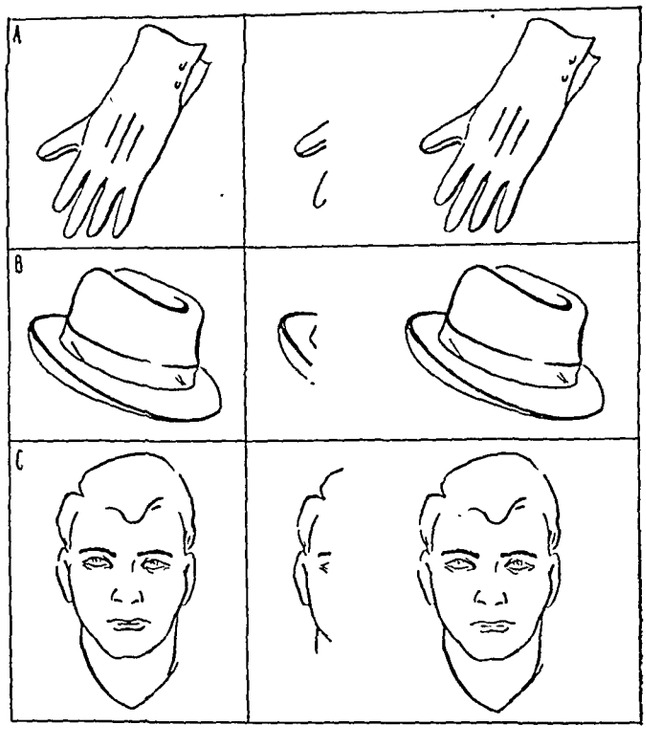



Fig. 8 (case 4).—Examples of what the patient saw (monocular diplopia) when he looked at symmetric objects and the face with his right eye. Columns are arranged as in figure 7.

thought it was an after-image, but he soon found that he could see the negative after-image in white, in addition to the black double image on the left. At times the negative after-image was on the right, but the second positive image, which was partial, was always on his left. For this reason, a battery of tests was given, and the observations which follow were made on testing the right eye; satisfactory studies could not be carried out on the left eye because here vision was poor.

1. The second, or false, image was always to the left and represented the extreme left portion of the original ground and figure exposed (fig. 7). It was always incomplete. At times the second image was situated on a slightly lower plane than the original image. The latency for the appearance of the second image was less than one second.

2. The diplopia was present for all types of objects he regarded: lines, geometric figures and drawings, faces, etc. (figs. 7, 8, 9 and 10).

3. The false, or partial, image always appeared fainter than the original image, even though it retained the color, contour and size of the left side of the original object exposed. The patient described the distinctness of the false image as being similar to that of the image which he perceived with the squinted eye. The right edge of the false image was never sharply demarcated and seemed to merge with the background.

4. The incomplete second image was seen even while the object was in motion (horizontal, vertical or circular motion). The false image of the object in motion was always incomplete and represented whatever there was on the left side of the original.

5. The monocular diplopia was present when the object was situated up to within 3 degrees of the fixation point. Beyond this visual angle, there was no diplopia except that for the fixation point itself.

6. The original and the partial image on the left generally kept their relationship in space as the object was moved from one point to another in the field of vision. The double images separated only when the original image was moved away from the patient.

7. Diplopia was present in any direction, and to some extent even for objects viewed at a distance, but the greatest amount of diplopia was for objects at a near point. The nearer the object was held to the patient, the more of the false image was visualized.

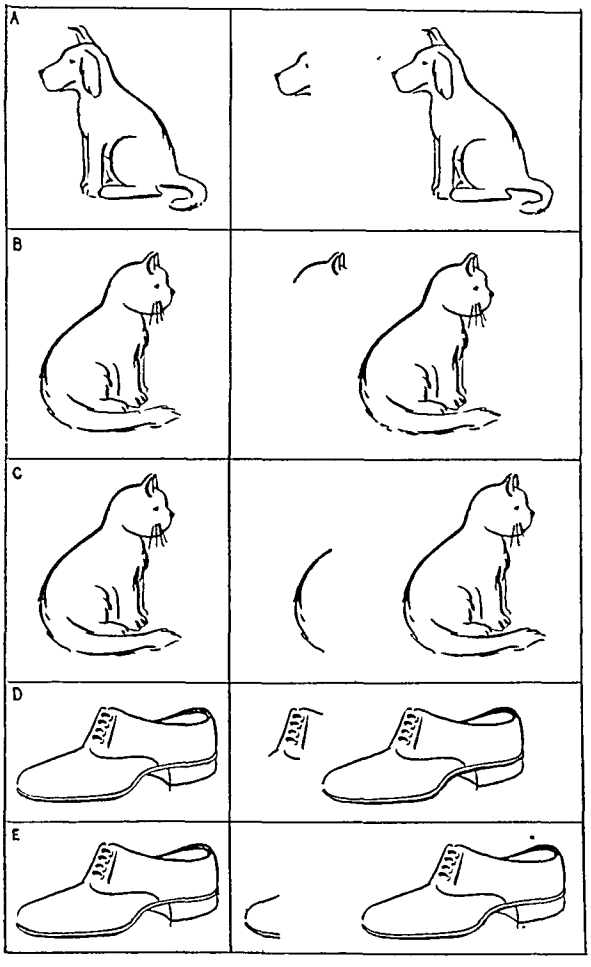



Fig. 9 (case 4).—Examples of what the patient saw (monocular diplopia) when he looked at asymmetric objects with his right eye. Columns are arranged as in figure 7.

8. When the original object was covered, the false image disappeared. At times the patient perceived both the negative visual after-images and the incomplete false image after prolonged fixation on the object; covering the original object abolished the false image but not the after-image.

9. When the patient regarded objects which were asymmetric in their contour, he saw different types of false images, depending on on which part of the object he fixed his vision. Thus, on looking at the dog in figure 9 *A*, he saw part of the snout to the left of the original. When he looked at the cat (fig. 9 *B*), he saw the ears and part of the head to the left. However, when he was asked to gaze at the middle of the cat, he saw the back in the false image (fig. 9 *C*). The same was true when he looked at the shoe (fig. 9 *D* and *E*). In other words the center of attention of the figure and ground attracted the patient's eyes, and this fixation point determined *what part of the original object appeared in the false* image.

10. On studying the Schröder staircase effect, the patient saw the extreme left part of the staircase to the left of the original. He found that the staircase fluctuated in its position and that the false image fluctuated *pari passu* with the original. When the picture looked like a staircase, he saw an additional step to the left of the original (fig. 10 *A*). When the stairs appeared inverted, like a cornice, he could not see the outline of the false image, although he felt something was there; the stair in the false image disappeared, and there was only a corner (fig. 10 *B*). When the stairs flipped back to the upright, or original, position, he saw the extreme left step in the false image.[28]

11. In order to analyze further the role of fixation and of ocular movements during fixation in this patient's monocular diplopia, the following experiments were performed: The patient's ocular movements were observed by three different methods (pinhole, mirror and after-image). All these studies revealed that the diplopia in the right eye occurred concurrently with lateral nystagmoid excursions of the globe during fixation. This was particularly evident with the method of after-imagery. The after-image of a small white luminous disk (produced by stimulating the patient's right eye with the ophthalmoscope) traveled horizontally to the left, starting slightly above the center of a red cross which the patient was instructed to fixate. These excursions repeated themselves until the after-image faded away. It was during these experiments that the patient discovered to his surprise that the excursion of the after-image (and the implied shift in fixation) invariably came to a halt vertically above the incomplete double image of the cross. This double, or false, image appeared as usual to the patient's left and slightly below the

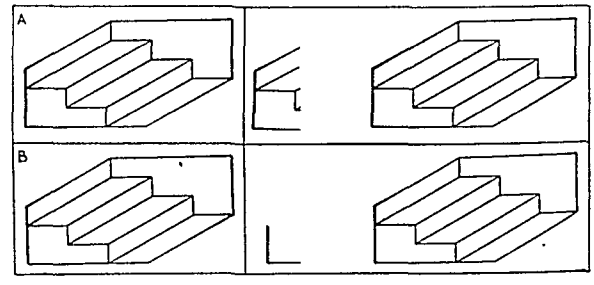



Fig. 10 (case 4).—Types of double images the patient saw when he looked at an object which fluctuated in its figure-ground relationship. Columns are arranged as in figure 7.

28. The patient thus gave a striking illustration of one of the main tenets of the Gestalt theory of perception, namely, that figure and ground are of necessity inseparable in percept formation (Köhler, W.: Dynamics in Psychology, New York, Liveright Publishing Corporation, 1940. Koffka, K.: Principles of Gestalt Psychology, New York, Harcourt, Brace and Company, Inc., 1935).

original. It always remained stationary and never shifted about, like the after-image.[29]

After one week the monocular diplopia diminished. It disappeared altogether in the left eye. (In this eye the diplopia was found only the first day and could be elicited with difficulty and never clearly.) At this time, the diplopia was found in the right eye only when the patient fixated with the globe or held the head in a certain position. With both eyes the patient continued to see double, but the pattern of the images was the same as that noted in the diplopia seen with the right eye. During the tenth week of his illness even the binocular diplopia had begun to disappear. However, when the right eye was tested repeatedly over a period of several hours, the monocular diplopia in this eye again became very apparent, and he was troubled with it for several days thereafter. The patient disliked being tested, as he feared recurrence of the diplopia.

*Comment.*—This patient had encephalitis following measles with clinical signs of involvement of the basal ganglia, hypothalamus, occipital lobes and probably many other parts of the brain. The syndrome of paralysis agitans and mental and other symptoms disappeared within a short period, but the visual troubles were most profound and lingered for some time. He showed disturbances in his visual Gestalt and after-imagery.

It is significant that the monocular diplopia (an original and an incomplete false image) appeared at about the same time that his ability to see after-images had returned. It is also significant that this patient had convergent strabismus. Since it is known that monocular diplopia may be induced in persons with squint, the question arises whether the patient did not induce a diplopia in himself by sensitizing the already diseased occipital lobe when he studied the negative after-images so avidly during the seventh week of his illness.[30] That such diplopia may have been induced in this case is suggested by the observation that repeated visual stimulation for tests of diplopia produced a recurrence of the symptoms during his period of recovery.

Another factor to consider is that of the spots about which the patient complained whenever he attempted to read or to regard an object. These spots were constantly present in his central field of vision and tended to interfere with his power of fixation. It is possible, therefore, that this disturbance in fixation was partly responsible for the monocular diplopia, especially since he already had a false macula in the left eye and thus probably an additional set of "space values" in the cortex.

The most unusual feature of all, however, was the incompleteness of the false image. The second image seemed to be a duplicate of the extreme left portion of the original, as though the original were covering all but the extreme left portion of the false image. This incompleteness of the false image may have been the reflection of a disturbance in his visual Gestalt, since the patient was unable to see the whole of a picture. He saw only individual parts. Whatever the mechanism for monocular diplopia may be, this is one example in which the second, or false, image is incomplete.

It is interesting to note that the false image was localized to the left. This was the side of his body and of his surroundings in space which represented poor vision, as symbolized by the amblyopia ex anopsia in the left, or strabismic, eye. Furthermore, the patient described the appearance of the false image as being similar to that which he had with the squinted eye. It is possible, therefore, that the second, or partial, false image represents the projected visual image of the psychologically defective left eye.

## COMMENT

The first 3 cases described in this report show several things in common, namely, (*a*) scotomas in the fields of vision; (*b*) fluctuation, obscuration or extinction phenomena in the defective fields of vision; (*c*) disturbance in the mechanism of fixation, and (*d*) optical illusions. The fourth case is somewhat different, inasmuch as there were no demonstrable field defects and the double, or false, image was incomplete. Naturally, the first impulse is to attribute all these symptoms to a common cause, but this is possible only from the structural standpoint.

One may safely assume that the scotomas were produced simply by damage to the calcarine cortex or the optic radiation. Here destruction of tissue produced absence of function. The rest of the symptoms, however, cannot be explained on a structural basis alone. They seem to be an expression of normal functions which become apparent only under pathologic conditions. Thus, in a previous communication, it was pointed out that fluctuation, obscuration and extinction of visual perception are psychologic phenomena which become evident in patients with diseases of the visual cortex or pathways.[15] This apparent disorder in perception is due to the presence, and not to a lack, of function.

29. Owing to the importance of these observations, the detailed discussion of them and of the methods employed will be given in a separate report. The after-image method for observation of ocular movements was used extensively by Helmholtz and other earlier physiologists (von Helmholtz H.: Handbuch der physiologischen Optik, Leipzig, L. Voss, 1911).

30. Tschermak, in 1899, and Sverdlick, in 1938, both of whom were cited by Cass,[4] considered the relationship between monocular diplopia and visual after-images.

Disturbances in the mechanism of fixation, as noted in the cases described here, are also expressions of underlying normal functions which are thrown out of equilibrium.

Fixation is maintained by a constant muscular effort in which the actions of all the ocular muscles are balanced. This constant activity results in fine rotatory movements, in which, although the globes may seem to be at rest, they are never completely immobile. According to Duke-Elder,[31] three types of movements are evident in the act of fixation; (*a*) relatively large, jerky excursions through an average angle of 4 minutes or more, recurring at intervals of from one to two and one-half seconds; (*b*) in the interval between these, when the eye appears at rest (the period of elementary fixation), a constant succession of much more rapid, fine, "twittering" excursions, through an angle of 1 minute, with a duration of one to two and one-half seconds, and (*c*) superimposed on these, a minute variation in the position of the head. As a consequence of these movements, the region of the retina which is used in fixation, i. e., the fovea, occupies a considerable area. These movements occur equally in each eye, whether used for near or distant vision or whether one or both eyes are employed in fixation. These movements vary considerably with each subject, with the state of adaptation of the eye and with illumination. Such constant movement, although not apparent, is important in the physiology of vision and is pertinent to the discussion of monocular diplopia and polyopia.

It is probable that the continual movement of the globe during fixation leads to stimulation of more than one retinal point in the fovea. If there happens to be a disturbance in the mechanism of fixation, the movements of the eyes are more pronounced, and slight ocular deviations may become grossly apparent.

Now, one of the chief causes of disturbance in the mechanism of ocular fixation is disease of the occipital lobe. The occipital lobes are largely responsible for initiating movements in the eyes which bring them into a position of fixation. When one of the lobes is defunct or loses its influence on the position of the eyes, the normal occipital cortex is unopposed in its function, and there results an imbalance between the opposing forces. During the act of fixation, impulses reach the normal side and tend to pull the eyes in that direction without opposition from its antagonistic, but diseased, side. If the deviation is slight, the patient is unaware of it, even though the retinal image falls on a new fovea.

31. Duke-Elder, W. S.: Text Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, p. 589.

Another cause of defective fixation is the phenomenon of visual extinction. When an image from a defective field of vision fluctuates in its appearance, or becomes obscure, or even extinct, as a result of competition between the healthy and the diseased side of the brain, the associated reflex visuomotor reactions come into operation, with resultant domination in motor function by the normal side. This imbalance in motor influence produces a tonic deviation of the head and eyes, and, because the image cannot fall on the true macula, there is further difficulty in fixation. Whatever the cause of dysfunction in the mechanism of fixation may be, the reflex and unconscious ocular deviation will cause the image of the regarded object to fall on a retinal point other than the true macula and thus form a new, or false, macula. If this new point is near the true macula and the constant and rapid ocular movements which occur during the act of fixation are such that both the true and the false macula are stimulated within a fraction of a second of each other, there results a conflict between the visual sensations thus evoked at the two retinal points. Such a conflict will result in defective vision, in the formation of more than one image, or in normal vision if the true macula dominates over the false. This leads to the discussion of the fourth common symptom in the group of cases herein reported, namely, monocular diplopia and polyopia. In an attempt to explain these optical illusions it is necessary to consider the physiologic and psychologic components of the fields of vision.

The ability to localize the position of an object in space depends not only on vision but on tactile, postural and labyrinthine sensations. All of these body sensibilities are integrated into a scheme which is represented in the brain, and this, in turn, is oriented in relation to the scheme of the external world. Visual localization is a process which involves (1) a relative factor, or localization of an object relative to the fixation point, and (2) an absolute factor, or localization of the fixation point with reference to the observer. The position of each stimulated visual point acts on the "mind," [32] and the relation of all the visual localization points is maintained in the cortex. The fovea forms the primary point of reference, and the images formed thereon are projected on a line which passes outward through the nodal point of the eye, or the fixation line. About this point of reference the field of vision is so spatially organized that the person is aware of a "right," "left," "up" and "down" and

32. Sherrington, C.: The Proprioceptive Function of the Extrinsic Ocular Muscles, Brain **41**:332-343, 1918.

the center, which is "straight forward" or "just before me." The center of the field determines the subjective median point. In the normal person, the latter coincides with the objective median zone, or the macular region. This entire scheme of the perceptive field of vision is also projected on the occipital cortex.

In patients with squint or with scotoma involving the macula, the subjective median plane is displaced, and there is no longer correspondence between it and the objective median zone. When there is weakness of the eye muscle or faulty fixation, either of which produces slight ocular deviation, the image of the regarded object is projected on a new macula. This, in turn, leads to a reorganization of the perceptive field of vision about the new macula. The functional values of points in the retina change and rearrange themselves in relation to the new macula, thus forming a new center of distinctness. In other words, the patient learns to use a new fovea. The location of the new fovea is not fixed and may not be far away from the old, or congenital, fovea. The distance between the anatomic and the functional fovea is determined largely by the Gestalt of the object.[33]

With the establishment of a new macula and its consequent reorganization of the field of vision, there occurs a corresponding change in the occipital cortex. Stimulation of the new macula leads to perception of an object, just as stimulation of the old macula did.

If both maculas are stimulated simultaneously, diplopia results. In cases of congenital squint the images obtained from the squinted eye are psychologically suppressed, and there is no binocular vision. But if the true and the false maculas of the squinted eye are stimulated simultaneously, as demonstrated by Cass, monocular diplopia will appear. In cases in which there is faulty fixation, and therefore more than one functional macula, the rapid movement of the eyes during the act of fixation might produce the effect of simultaneous stimulation of the true and the false macula, with resultant monocular diplopia. The same analogy holds for polyopia, in which several new functional maculas have been established in the cortex.

That monocular diplopia and polyopia are largely due to development of new maculas and faulty fixation is well illustrated in cases 3 and 4. In case 3, the illusion was present only within 2 degrees of the median point, when the exposed object was situated within 63 cm. of the projected line of fixation, and it did not appear unless the patient attempted to focus on the object. Furthermore, he had difficulty in maintaining his gaze, since there was a conflict between the right (normal) and the left (pathologic) field of vision.

In case 4, the monocular diplopia was also limited to the foveal area. On several occasions the patient had to turn his head and eyes and focus on the object in a certain position before the diplopia appeared. Furthermore, direct observation by three different methods revealed nystagmoid movements during fixation, and it was during the movements of fixation that the monocular diplopia became apparent. Although he showed no demonstrable field defect, he had a subjective scotoma about his fixation point. He complained that the spots before his eyes (in the subjective median plane) covered part of the print and he could not see clearly. This implied that in his attempt to see "better" he tried to fix on the object in some manner, thus revealing a disturbance in fixation, and it is also probable that because of the subjective scotoma a new macula may have formed.

The patients in cases 1 and 2, although not studied while they had polyopia, gave a history, and later showed residual signs, of difficulty in fixation and visual defects, with probable formation of new maculas. In case 2, the more the patient tried to fix on an object, the more blurred and multiple it appeared. The quadruplopia, with images appearing in the vertical and horizontal meridians, as described in case 1, may have been due to the partially altitudinal and partially lateral hemianoptic field defects. It is possible that the altitudinal defect produced a reflex deviation of the eyes in the vertical plane and thus led to formation of double images in this direction, in the same manner as lateral hemianopsia produces diplopia or polyopia along the horizontal meridian.

On the basis of the observations made in the cases reported here, it is apparent that monocular diplopia and polyopia are indirectly attributable to imperfect fixation. As already pointed out, defective macular vision leads to difficulty in ability to fixate, and, conversely, imperfect fixation stimulates the formation of new maculas. In either instance, the power to maintain the eyes on a given point is impaired, and this, in turn, creates an increase in the amplitude of the ocular excursions normally present during the act of fixation. Such an increase in ocular movements will, in effect, cause different macular points in the foveal area to be stimu-

33. Fuchs, W.: Untersuchungen über das Sehen der Hemianopiker und Hemiamblyopiker: I. Verlagerungserscheinungen, Ztschr. f. Psychol. u. Physiol. d. Sinnesorg. **84**:67-169, 1920; II. Die totalisierende Gestaltauffassung, ibid. **86**:1-143, 1921.

lated repeatedly and at a rapid rate, with consequent activation of their functional centers and the corresponding space values. An analogous situation can be found in cases of cutaneous sensory disorders in which repeated stimulation of a functionally disorganized area evokes more than one sensation (synesthesia). From these considerations one may deduce the theory that it is the repeated stimulation of a functionally disorganized sensory area which "fires off," or activates, more than one functional center (and space values) at a time, thus yielding multiple images. Although this does not disprove Goldstein's contention of "diffusion of an excitation" in the cortex, it is felt that this theory adequately explains monocular diplopia and polyopia.

In general, it would seem that multiple image formation is due to a disorganization in function produced by disease of structure.. Since monocular diplopia and polyopia are the result of a dynamic disequilibrium in psychologic visual functions, it is readily understood why these symptoms are often so transient. The organism learns to correct its seeing of an abnormal number of images by selecting or finding one of the several available maculas and assigning to it all the sensory and motor attributes necessary to keep it as the dominant central point in its newly organized field of vision.

## SUMMARY

Cases of objective and subjective disturbances in the visual fields with associated defects in mechanisms of fixation are described. The patients had either monocular diplopia or polyopia or both, and some of them also had symptoms of spatial disorientation. It is concluded that the rapid and involuntary movements of the eyes produced by faulty fixation tend to stimulate, simultaneously, the original macula and any new maculas which may have been formed as a result of impairment of vision.

United States Naval Hospital, San Diego, Calif.

# THE HUMAN PYRAMIDAL TRACT

## XIII. A STUDY OF THE PYRAMIDS IN CASES OF ACUTE AND CHRONIC VASCULAR LESIONS OF THE BRAIN

A. M. LASSEK, PH.D., M.D.
CHARLESTON, S. C.

The purpose of the present investigation is to correlate as nearly as possible the motor deficits produced in striated muscles by cerebrovascular lesions with axonal destruction in the pyramids. Such injuries, in the form of emboli, thromboses or hemorrhages, are known to have a destructive action on nerve tissue. It may be possible that these three forms of vascular disturbance do not act in exactly the same manner on the neurons of the pyramidal tract. Wide variations in the extent and potency of each type may be the rule. Although it appears that the true status of the cerebral collateral circulation has not been definitely settled, this vascular supply may be a factor in maintaining the viability of neurons under certain pathologic conditions, especially those of the thrombotic type. All of these factors may be reflected in the damage done to the axons of the pyramidal tract.

The pyramidal fasciculus is regarded as one of the most susceptible to disease processes in the central nervous system. This view has been formulated largely on the results of comparative phylogenetic and ontogenetic studies of nerve tracts, which, in turn, have been correlated with the frequency of clinical involvement of the tracts. On this basis, the pyramidal pathway should be preeminently unstable and easily destroyed, since it is the last to appear in the animal scale and, also, in the individual development of the human.

Paralysis is a common clinical symptom which has always been associated with destruction of the pyramidal tract. The question arises as to how much fiber loss is necessary to produce muscular disability. Apparently, few detailed and specific studies have been made in this respect. Supratentorial vascular lesions must always occur in the region of complex cell and fiber structures, i. e., the cerebral cortex, the internal capsule, the association bundles, the thalamus, the corpus striatum, the substantia nigra and the claustrum. It is estimated that there are about 12,000,000,000 cells in the cerebral cortex alone, and each must give origin to an axis-cylinder, according to the neuron theory. Involvement of nonpyramidal motor and sensory fibers may, therefore, be relatively great with the majority of high vascular lesions. The pyramidal fibers may comprise but a small percentage of the total number destroyed in the majority of cerebrovascular insults.

The following characteristics make the pyramidal tract acceptable for the present problem: It is regarded as the great voluntary motor tract; it has a central origin from the cerebral cortex; it occupies a midposition in the internal capsule; it is almost completely isolated in its course through the pyramid, and it is supplied by all the vessels which course to the brain, including the lenticulostriate artery.

### MATERIAL AND METHODS

The study consists in an analysis of 106 selected cases of vascular lesions obtained through the cooperation of several neuropathologic departments. The hospitals, with the number of cases contributed, are listed as follows: Montefiore Hospital, 22 cases; Philadelphia General Hospital, 19 cases; Cincinnati General Hospital, 17 cases; Barnes Hospital, St. Louis, 15 cases; Neurological Institute of New York, 14 cases; Mount Sinai Hospital, New York, 14 cases, and Welfare Island, N. Y., 5 cases.[1]

Fifty-eight patients were males; 44 were females, and the sex of 4 could not be determined. The average age was 53.3 years. In all of the 106 cases some form of motor deficit existed, with one or more of the classic signs referable to the pyramidal tract. In 55 cases a clinical diagnosis of hemiplegia was made; in 19 the clinical sign was hemiparesis, while in the remaining 32 cases the diagnosis was made under various terms such as paralysis, loss of muscular power,

From the Department of Anatomy, Medical College of the State of South Carolina.

Aided by a grant from the Committee of Scientific Investigation of the American Medical Association.

1. The following physicians cooperated in making available the material for this study: Dr. C. D. Aring, of the Cincinnati General Hospital; Dr. Charles Davison, of Montefiore Hospital, New York; Dr. J. H. Globus, of Mount Sinai Hospital, New York; Dr. Helena E. Riggs, of Philadelphia General Hospital; Dr. W. O. Russell, of Barnes Hospital, St. Louis, and Dr. A. Wolf, of the Neurological Institute of New York.

limping or weakness. In 69 cases the condition was judged to be of the chronic and in 37 of the acute type. The duration of motor symptoms varied from three days to twenty-one years, the average being two and a half years. In any case in which symptoms of muscular disability were in evidence longer than two months the disturbance was classified as chronic irrespective of other disease symptoms. Recurrent strokes occurred in some cases. In 40 cases a Babinski sign was elicited at some stage of the paralysis; in 7 cases there was a questionable Babinski sign; in 4 cases there was an Oppenheim sign; in 2 cases a Hoffmann reflex was recorded; in 3 cases the clinicians stated definitely that there was no Babinski sign present; in 1 case signs of involvement of the pyramidal tract were recorded by the observer, and, finally, in 49 cases no report was made as to the status of the pathologic toe reflexes.

The pathologic diagnoses of the cerebrovascular lesions were as follows: subarachnoid hemorrhage, emboli, thrombi, intracranial hemorrhage, softening, encephalomalacia, cystic malacia, chronic hematoma, ruptured aneurysm, venous thrombosis and hemorrhagic infarct.

Only the pyramids of the medulla oblongata were examined. The specimens were all fixed in dilute solution of formaldehyde U. S. P., and the axons were stained with Davenport's silver nitrate method in the first stage of the investigation and with Bodian's technic later. The Loyez method was employed for staining myelin sheaths in about one-half the specimens. In some cases sudan III was employed for fat. More reliance was placed on the sections stained with the silver methods.[2] For various reasons, no standard level of the medulla could be examined. In some instances both cross and longitudinal sections were examined, but the majority of sections were in the former group. The amount of fiber loss was merely estimated in all cases.

## RESULTS

In 7 of the series of 106 cases,[2] complete destruction of the pyramidal tract was indicated by a study of the pyramids. In 36 other cases there were varying amounts of degeneration, ranging from slight to almost complete. In the remaining 63 cases there was no overt evidence of a degenerative process. In the last group it is possible that some fibers may have been missing or slightly altered, so that changes could not be ascertained from microscopic examination. If this were true, however, it would seem that the loss would be minimal.

The following 11 cases in the series illustrate the signs, symptoms and pathologic changes, in all of which there was no evidence of destruction of the pyramidal tract.

CASE 1.—A woman aged 58 was admitted on Nov. 2, 1939 and died November 25.

*History.*—Right hemiplegia with aphasia developed five years prior to her admission to the hospital. A second episode, also with aphasia, occurred two years previously.

*Examination.*—Palsy of the right side of the face of the upper motor neuron type was observed. The tongue deviated to the right. Motor weakness of the right upper and lower extremities was present. The abdominal reflexes were absent on the right side. Hoffmann and Rossolimo signs were present on the right side. A suprapatellar clonus was elicited on the same side. There was definite motor aphasia.

*Course.*—The patient suffered a third vascular accident on November 23. At this time she had left hemiplegia with weakness of the left side of the face of central type. The deep reflexes were much stronger on the right side than on the left. Abdominal reflexes were not elicited. The feet were in the chronic Babinski position, and there was a marked grasp reflex on the right. The patient died two days later.

The duration of motor symptoms was five years.

*Autopsy.*—A large subarachnoid hemorrhage extended over part of the motor, parietal and superior temporal convolutions. A frank hemorrhage involved the white and gray matter of the superior part of the motor, the inferior parietal and the temporal convolutions.

*Microscopic Diagnosis.*—The diagnosis was generalized cerebral arteriosclerosis, hypertension and hemorrhage along the distribution of the right cerebral artery.

*Examination of the Pyramids.*—There was no observable loss of axons in the pyramidal tract.

CASE 2.—A woman, whose age was not given, was admitted to the hospital Sept. 20, 1937 and died Jan. 2, 1939.

*History.*—In 1934 the patient had an episode of unconsciousness, followed by inability to use the left leg.

*Examination.*—There were hyperactive reflexes, loss of abdominal reflexes, a bilateral Babinski sign and a questionable Chaddock sign on the right side.

*Course.*—On Oct. 1, 1937 examination showed left-sided hyperreflexia, absence of the Babinski sign, positive Mendel-Bechterew and Rossolimo signs on the left and weakness of the left upper and lower extremities.

The duration of motor symptoms was five years.

*Autopsy.*—A small area of softening in the right cerebellar hemisphere involved the lobulus ansiformis crus II. There was a slight area of softening in the right paracentral lobule.

*Microscopic Diagnosis.*—The diagnosis was embolism of the paracentral branch of the right middle cerebral artery and branches of the posterior inferior cerebellar artery.

*Examination of Pyramids.*—There was no observable loss of axons in the pyramidal tract.

CASE 3.—A man aged 60 was admitted Feb. 24, 1939 and died Jan. 12, 1940.

*History.*—The patient had noted weakness of the left arm and leg for the past six months.

*Examination.*—At the time of admittance examination revealed essentially no motor deficit.

*Course.*—On Nov. 1, 1939, the patient was suddenly unable to talk; the right corner of his mouth drooped, and he was unable to move his right arm and leg. The weakness of the right upper extremity was of flaccid type. Ankle clonus was elicited on the right side. Abdominal reflexes were absent on the right. The Oppenheim sign was present on the right side but no other pathologic plantar responses were elicited. There was weakness of the right side of the face of central type. The aphasia improved somewhat.

The duration of symptoms was seven months.

2. Miss Iseult V. Finlay and Miss Margaret Powers carried out all phases of the technical staining procedures.

*Autopsy.*—An area of softening was found in the posterior part of the third frontal convolution, at the base of the premotor, motor and parietal convolutions and possibly in part of the superior temporal convolution on the left side. Microscopic examination verified the gross observation and, in addition, showed that the island of Reil, the external capsule, the putamen and part of the internal capsule on the same side were also involved. The gray and the white matter were equally affected. The microscopic diagnosis was thrombosis of the left middle cerebral artery and branches of the left posterior cerebral artery, as well as generalized cerebral arteriosclerosis.

*Examination of the Pyramids.*—Silver-stained sections revealed no observable fiber loss.

CASE 4.—A woman aged 53 was admitted on June 4, 1940 and died November 12.

*History.*—Four weeks before admission the patient awoke in the morning and found her right arm and leg were weak.

*Examination.*—There were slight flaccid paresis of the right extremities, defective plantar responses bilaterally and absence of abdominal reflexes.

*Course.*—The duration of motor symptoms was seven months.

*Autopsy.*—There was a small area of softening in the region of the pulvinar of the thalamus on the left side. Microscopically, some of the fibers between the pulvinar and the medial lemniscus were completely destroyed. Fibers emerging from the dentate nucleus showed fragmentation, swelling and disintegration of myelin.

The microscopic diagnosis was thrombosis of a branch of the left posterior cerebral artery and emboli to branches of the superior cerebellar artery.

*Examination of the Pyramids.*—There was no evidence of a degenerative process in the axis-cylinders.

CASE 5.—A man aged 64 was admitted on June 20, 1936 and died on April 6, 1941.

*History.*—A staggering gait developed in March 1936, three months before the patient's admission. Shortly afterward the patient noted that the left upper and lower extremities were weak and that the mouth was drawn to the right. He was hospitalized for six weeks, during which time there was some increase in power on the left side. After his discharge his left extremities became weaker.

*Examination.*—Examination revealed left hemiparesis, impairment of skilled movements in the left hand, deep hyperreflexia on the left side; absence of the abdominal reflexes; Babinski, Chaddock, Oppenheim and Rossolimo signs on the left; a questionable Babinski sign on the right; slight paresis of the muscles of the jaw on the left side; paresis of the left lower part of the face; paresis of the left half of the palate, and deviation of the tongue to the left on protrusion.

*Course.*—On April 5, 1941, one day before his death, it was noted that the hemiplegia was marked on the left side.

The duration of motor symptoms was five years.

*Autopsy.*—A massive hemorrhage was present in the right cerebral hemisphere, involving essentially the white matter along the island of Reil and destroying practically all of it, the external capsule, the claustrum, the putamen, part of the internal capsule and part of the thalamic nuclei. There were hemorrhages in the tegmentum, extending from the aqueduct to the fourth ventricle, which was filled with hemorrhagic material.

*Microscopic Diagnosis.*—The diagnosis was hemorrhage or rupture of the right middle cerebral artery and branches of the basilar arteries; thrombosis of the left posterior inferior cerebellar artery; subarachnoid and intraventricular hemorrhages, and generalized cerebral arteriosclerosis.

*Examination of the Pyramid.*—There was no evidence of degeneration in the axons of the pyramidal tract.

CASE 6.—A man aged 59 was admitted June 26, 1936 and died June 29.

*History.*—The chief complaint of the patient was staggering gait. On Jan. 2, 1936, more than six months prior to admission, the patient experienced loss of consciousness and paralysis of the right side of the tongue. He was unable to stand for several days. On January 24 he was able to walk, with a staggering gait. On June 26, there was a repetition of the stroke and he was admitted to the hospital in a critical condition.

The duration of symptoms was seven months.

*Autopsy.*—A spherical cystic lesion, 8 mm. in diameter, occurred at the junction of the anterior and the posterior arm of the left internal capsule and extended into the lateral nucleus of the thalamus. A second, oval, cyst, 8 by 3 by 4 mm., was located in the centrum ovale of the right frontal lobe, just lateral to the corpus callosum. A third cyst, smaller than the second, was found just beneath the tip of the frontal horn of the left ventricle. All these cysts appeared not to be of recent origin.

*Examination of the Pyramids.*—No loss of axons in the pyramidal tract was observed.

CASE 7.—A man aged 47 was admitted with the chief complaint of right-sided hemiparesis on July 30, 1937 and died August 23.

*History.*—In May 1936, fourteen months prior to admission, the patient was found unconscious, with complete paralysis and inability to speak. Three weeks later speech and motor power began to return.

*Examination.*—There was clubbing of the fingers. The right arm was adducted, whereas the gait was normal. Associated movements of the right arm were almost absent. The right arm was atonic and flaccid. Speech was halting and thick. The abdominal reflexes were absent on the right side. No other abnormality of the reflexes was noted.

The duration of symptoms was fourteen months.

*Autopsy.*—Encephalomalacia involved the precentral, the postcentral and the posterior end of the superior frontal gyrus on the left side. Microscopic examination showed complete disappearance of the ganglion cells. There were no changes of note in the pons or the medulla. The probable diagnosis was embolus of the middle cerebral artery. The Betz cells may have been preserved.

*Examination of the Pyramids.*—No loss of axons was noted.

CASE 8.—A woman aged 51 was admitted Sept. 3, 1937, with staggering gait. She died October 8.

*History.*—In September 1936 there were noted wabbling gait and weakness of both lower extremities, with increased fatigability. By December 1936 she could walk only with support and since then had fallen a number of times when trying to walk.

*Examination.*—The patient was able to walk only with support, and then on a wide base and with marked unsteadiness. There was slight clumsiness of both hands, the left being more affected than the right. A Babinski sign was elicited on the right.

*Course.*—A suboccipital craniotomy was performed on Oct. 4, 1937.

The duration of symptoms was one year.

*Autopsy.*—The only observations of note were hemorrhage and vacuolation in the reticular formation of the midbrain and the pons.

*Examination of Pyramids.*—No loss of axons was noted.

CASE 9.—A man aged 59 was admitted Dec. 20, 1938 and died Jan. 3, 1939.

*History.*—The patient had had a stroke involving the right side one year before admittance to the hospital. Strength had gradually but never completely returned.

*Examination.*—There were paresis of the right side of the face and partial paralysis of the left side of the face of central type. The patient could move his left arm only slightly and could not grip with the left hand. He moved the right arm fairly well but with definite weakness. There was weak motion in both legs, the left being affected more than the right. Muscular tone was increased bilaterally. The tendon reflexes were increased. The abdominal reflexes were absent on the left. The cremasteric reflexes were absent. All pathologic toe signs were present bilaterally.

*Course.*—A second stroke occurred the night before death.

The duration of motor symptoms was one year.

*Autopsy.*—There was an old area of softening in the left inferior frontal gyrus. A similar area of old softening, corresponding to that described on the surface, involved the right precentral gyrus and the adjacent inferior frontal gyrus. A third area of old encephalomalacia, measuring approximately 1 by 0.25 cm. in cross section and 1.5 cm. anteroposteriorly, was present in the posterior extremity of the left putamen. It was cystic and light brown. There were no changes of note in the midbrain, pons or medulla.

*Examination of the Pyramids.*—There was no evidence of degeneration of axons in the pyramidal tract.

CASE 10.—A woman aged 53 was admitted July 17, 1939.

*History.*—Weakness of the left side of the body followed an operation for hysterectomy four months prior to her admission. Shortly after the operation left hemiplegia developed; this condition steadily improved.

*Examination.*—There were almost complete paralysis of the left arm and paresis of the left leg. No changes were noted in the deep reflexes, and the Babinski sign was not elicited.

*Course.*—During the patient's stay in the hospital, the left hemiplegia gradually disappeared. She died Sept. 14, 1939, about two months after admittance.

The duration of symptoms was six months.

*Autopsy.*—The white matter of the right cerebral hemisphere contained a few small zones of cystic malacia, and in these areas there was partial destruction of neural and glial elements.

*Examination of the Pyramids.*—There was no evidence of loss of axons in the pyramidal tract.

CASE 11.—A woman aged 52 was admitted with left-sided weakness on Sept. 25, 1941 and died October 15.

*History.*—In the fall of 1940 there developed weakness of the left lower limb and awkwardness of the left hand, which persisted and grew progressively worse.

*Examination.*—The gait was unsteady, and the patient was unable to walk on the heels or the toes. There was slight weakness of the left upper limb. Ankle clonus and a Babinski sign were elicited on the left. The deep reflexes were overactive bilaterally, and the abdominal reflexes were reduced bilaterally.

*Course.*—On Oct. 9, 1941, the patient was unable to walk, and the left hemiplegia became more pronounced.

The duration of symptoms was about one year.

*Autopsy.*—A macerated area occupied the right superior parietal lobule, the dorsal extremity of the transverse occipital gyrus and the cuneus. Hemorrhage into this area was observed. There was a herniation of the gyrus cingulus. The cerebral peduncles were displaced slightly toward the left. No changes of note were observed in the nuclei or the tracts of the medulla or pons. The cerebellar tonsils were herniated through the foramen magnum.

*Examination of the Pyramids.*—No degeneration of axons was noted.

## COMMENT

If destruction of pyramidal tract fibers is the predominant cause of hemiparesis or hemiplegia, then I believe that it requires little or no loss of fibers of this tract to produce this symptom complex. This conclusion is based on the results of study of the pyramidal tract fibers in the pyramids in about 260 cases of paralysis caused by cerebral tumors and cerebrovascular injuries. Complete destruction of the pyramidal tract fibers in such cases is the exception rather than the rule. There are relatively many more cases in which there is no evidence of destruction. In the present series of 106 cases of vascular lesions, complete destruction occurred in 7, partial and variable loss of fibers in 36 and no microscopic evidence of a degenerative process in the pyramids in the remaining 63 cases.

There is abundant evidence in the literature that the pyramidal tract is one of the most delicate and susceptible tracts in the central nervous system. This viewpoint was originally expressed by the Netherland school of neurologists, and it has been correlated with the late phylogenetic and ontogenetic development of the bundle. From the evidence at hand, it would appear that the pyramidal tract fibers are difficult to destroy completely. If this is true, this tract should be a durable group of fibers. This does not mean that its physiology may not be interefered with when no destruction is discernible. Inhibition of nerve conduction may possibly be a factor in causing neural dysfunction.

An important question in neuropathology would seem to be the length of time it requires for disappearance of pyramidal tract fibers in man after maximum injury of their cells of origin or of their nerve fibers. Different pathologic processes might affect nerve fibers differently,

one pathologic entity destroying rapidly and another more slowly. Thrombosis, embolism and hemorrhages in themselves might not act in the same way in this respect. I have a case, recorded as one of complete left hemiplegia, in which the pyramidal tract is shown to have been completely destroyed five weeks after the onset of symptoms. In this laboratory, my colleagues and I have obtained rather complete degeneration of pyramidal fibers in the pyramids in the monkey in nineteen days and in the cat in six days after large scale removal of the cortex. Again, experimental cortical ablation may be an entirely different process than that which occurs in cases of cerebral tumor or vascular disease. I wish to be cautious and conservative in analyzing the pathologic data for man.

It is difficult to say what the exact role of the pyramidal tract is in total hemiplegia or complete paralysis. In many cases of cerebral tumors and cerebrovascular disease with chronic motor deficit in the striated muscles there is no overt evidence of destruction of the pyramidal tract. Cases of repeated strokes which produce transient hemiplegias likewise may fall into this category. Whether the neurons have not been involved in the pathologic process, whether they have survived the direct effects of the lesion or whether temporary or relatively lasting inhibition of neural activity over the pyramidal bundle may be factors, I am unable to say.

It is realized that there may be certain limitations involved in the material used in the investigation. Many observers participated in working out the histories, in giving the neurologic examinations and in analyzing the pathologic data. It may be that in most instances their attention was not focused directly on the pyramidal tract. In the absence of any investigations limited directly to the problem, it is believed that the over-all observations may be suggestive that massive or all-inclusive neuronal destruction of the pyramidal tract is not the main pathologic factor in the majority of cases of paralysis. It is hoped that further investigations in suitable neurologic centers may be carried out in this field, special attention being paid to the extent and nature of the lesion in the region of the known elements of the pyramidal system.

## SUMMARY AND CONCLUSIONS

Hemiparesis or hemiplegia, caused by chronic vascular lesions, can occur with little or no destruction of the fibers of the pyramidal tract.

In a series of 106 persons who died of cerebrovascular disease, 7 showed complete destruction of the axons within the pyramid, 36 exhibited varying amounts of degeneration and 63 gave no overt evidence of a degenerative process.

Patients having transient hemiplegias during life due to vascular insults may exhibit no loss of fibers of the pyramidal tract post mortem. This may explain, in part, the restitution of function in these patients.

In general, cerebrovascular lesions produce more destruction of axons of the pyramidal tract than do cerebral tumors.

In contrast to the prevailing opinion, the neurons of the pyramidal tract appear to be durable and difficult to destroy completely.

Medical College of the State of South Carolina 16.

# BILATERAL INTRACRANIAL SECTION OF THE GLOSSOPHARYNGEAL NERVE

## REPORT OF A CASE

HENRY WYCIS, M.D.
PHILADELPHIA

Unilateral intracranial division of the glossopharyngeal nerve is indicated in cases of glossopharyngeal tic, hypersensitive carotid sinus syndrome and malignant growths of the nasopharynx.

A case of glossopharyngeal pain was first recorded by Weisenburg,[1] in 1910. Autopsy in this case disclosed a tumor of the posterior fossa involving primarily the ninth cranial nerve. In 1920 Sicard and Robineau [2] recorded 3 cases of true glossopharyngeal neuralgia. They asserted that the pain was due to involvement of the ninth and tenth cranial nerves and the superior cervical sympathetic ganglion. In 1921 Harris [3] introduced the term glossopharyngeal neuralgia and described 2 cases. A great deal of confusion arose at this time as to whether the glossopharyngeal nerve was motor or sensory or both. Vernet [4] taught that the glossopharyngeal nerve was largely motor in function and that sensation to the pharynx and soft palate was supplied by the vagus nerve. Dandy,[5] in 1927, showed that by intracranial division of the ninth cranial nerve glossopharyngeal pain could be relieved. He attempted to demonstrate that the glossopharyngeal nerve was entirely sensory and that it supplied the nasopharynx, the posterior pharyngeal wall to the epiglottis, the tonsil, the soft palate and the posterior third of the tongue. The salivary glands receive a parasympathetic motor outflow, and it was shown by Reichert and Poth [6] that after section of the glossopharyngeal nerve temporary suppression of salivation resulted. Because of Vernet's teaching, Sicard and Robineau,[2] Doyle [7] and Adson [8] sectioned the ninth and tenth cranial nerves and sympathetic nerves. It remained for Dandy [5] to outline the rational treatment for glossopharyngeal tic, although Adson had planned such a procedure three years earlier. Since the introduction of Dandy's operation, numerous neurosurgeons have adopted the procedure for relief of glossopharyngeal tic. The trigger zone in cases of this disorder lies in the tonsillar area, although in occasional cases a second trigger point may be found in the external auditory canal. In such instances it is apparently necessary to section not only the glossopharyngeal nerve but the superior rootlets of the vagus nerve. Such cases have been reported by McKenzie and Keith [9] and by Spurling and Grantham.[10]

Since the pioneer work by Weiss and Baker [11] in 1933 on the hypersensitive carotid sinus syndrome, several reports [12] have appeared in the

From Temple University Hospital and Medical School.

1. Weisenburg, T. H.: Cerebello-Pontile Tumor Diagnosed for Six Years as Tic Douloureux: The Symptoms of Irritation of the Ninth and Twelfth Cranial Nerves, J. A. M. A. **54**:1600-1604 (May 14) 1910.

2. Sicard, R., and Robineau: I. Algie vélo-pharyngée essentielle: Traitement chirurgical, Rev. neurol. **37**:256-257, 1920.

3. Harris, W.: Persistent Pain in Lesions of the Peripheral and Central Nervous System, Brit. M. J. **2**:896-900, 1921.

4. Vernet, M.: Syndrome du trou déchire postérieur (Paralysis des nerfs glossopharyngeal, pneumogastrique, spinal), Rev. neurol. **34**:117, 1918.

5. Dandy, W. E.: Glossopharyngeal Neuralgia (Tic Douloureux): Its Diagnosis and Treatment, Arch. Surg. **15**:198-214 (Aug.) 1927.

6. Reichert, F. L., and Poth, E. J.: Pathways for the Secretory Fibers of the Salivary Glands in Man, Proc. Soc. Exper. Biol. & Med. **30**:973-977, 1933.

7. Doyle, J. B.: A Study of Four Cases of Glossopharyngeal Neuralgia, Arch. Neurol. & Psychiat. **9**: 34-46 (Jan.) 1923.

8. Adson, A. W.: The Surgical Treatment of Glosso-Pharyngeal Neuralgia, Arch. Neurol. & Psychiat. **12**:487-506 (Nov.) 1924.

9. McKenzie, K. G., and Keith, W. S.: Report read before the Harvey Cushing Society, 1938.

10. Spurling, R. G., and Grantham, E. G.: Glossopharyngeal Neuralgia, South. M. J. **35**:509-513, 1942.

11. Weiss, S., and Baker, J. P.: The Carotid Sinus Reflex in Health and Disease: Its Role in Causation of Fainting and Convulsions, Medicine **12**:297-354, 1933.

12. (*a*) Bucy, P. C.: Carotid Sinus Nerve in Man, Arch. Int. Med. **58**:418-432 (Sept.) 1936. (*b*) Craig, W. M., and Smith, H. L.: The Surgical Treatment of Hypersensitive Carotid Sinus Reflexes: Thirteen Cases, Yale J. Biol. & Med. **11**:415-422, 1939. (*c*) Herbert, C.; Zahn, D.; Ryan, J., and Echlin, F.: Treatment of Carotid Sinus Sensitivity by Intracranial

*(Footnote continued on next page)*

literature dealing with surgical therapy of this entity. Weiss, Capps, Ferris and Munro [13] denervated the carotid sinus in 10 patients. They demonstrated a temporary, but distinct, increase in heart rate and blood pressure in their patients following this procedure. They had no opportunity to observe the effect of bilateral denervation on the level of the blood pressure. Unilateral intracranial section of the glossopharyngeal nerve for relief of the symptoms due to a hypersensitive carotid sinus has been reported on by Herbert, Zahn, Ryan and Echlin [12c] and by Ray and Stewart.[12d] The first group of workers stated the belief that intracranial section of the glossopharyngeal nerve completely denervated the carotid sinus, while Ray and Stewart showed conclusively that even after intracranial section of the ninth nerve procainization of the carotid sinus still caused a rise in blood pressure (2 cases). Of the 4 cases reported by Ray and Stewart, a temporary rise in blood pressure occurred in 3, while no significant changes appeared in the fourth case.

Section of the glossopharyngeal nerve for the relief of pain in the throat due to a malignant growth was first suggested and carried out by Fay.[14] This was in 1926, and use of the method for this purpose preceded Dandy's operation for glossopharyngeal tic. The procedure of intracranial section of the fifth and ninth cranial nerves and posterior cervical rhizotomy offers relief of pain in cases of malignant growths of the nasopharynx.

After the original investigation of Ludwig and Jarisch [15] on the depressor nerve and of Hering [16] on the carotid sinus, Koch and Mies [17] were able to demonstrate hypertension in experimental animals following bilateral section of the carotid sinus and the aortic depressor nerves (moderator nerves). The release of the cardiac and vasomotor centers from the influence of the moderator nerves permits these centers to exert a greater degree of cardiac acceleration and vasoconstriction. Not only had Heymans [18] confirmed this work, but he was able to produce and maintain arterial hypertension of 250 to 300 mm. of mercury for periods of nine to twenty-six months by section of the moderator nerves in dogs. Nowak and Walker [19] have reported an elevation of arterial blood pressure in dogs for as long as three years. The degree and duration of the hypertension depend, apparently, on the extensiveness of the operative procedure. Green, DeGroat and McDonald,[20] using a similar operative technic, were unable to duplicate Heymans' results in rabbits and dogs. Heymans stated that the failure to produce permanent hypertension in all dogs was due to the presence of accessory fibers in the cardioaortic nerves and to the presence of moderator, depressor influence in the pulmonary and intestinal pressor nerves. Complete removal of the paravertebral ganglionic chain can prevent or abolish this type of experimental hypertension (Heymans [18b]). It is of interest to note that the blood of these hypertensive dogs has a higher degree of vasopressor activity than has that of normal controls (Heymans and Bouckaert [21]).

In man, Bucy [12a] was the first person to demonstrate hypertension by intracranial division of the glossopharyngeal nerve. Ask-Upmark,[22] a year earlier, had demonstrated a sharp and immediate rise in blood pressure following denervation of the carotid sinus. However, he had failed to make any prolonged observations in his

Section of the Glossopharyngeal Nerve, Tr. Am. Neurol. A. **68**:29-31, 1942. (*d*) Ray, B. S., and Stewart, H. J.: Observations and Surgical Aspects of the Carotid Sinus Reflex in Man, Surgery **11**:915-938, 1942.

13. Weiss, S.; Capps, R. B.; Ferris, E. B., Jr., and Munro, D.: Syncope and Convulsions Due to Hyperactive Carotid Sinus Reflex: Diagnosis and Treatment, Arch. Int. Med. **58**: 407-417 (Sept.) 1936.

14. Fay, T.: Intracranial Division of Glossopharyngeal Nerve Combined with Cervical Rhizotomy for Pain in Inoperable Carcinoma of the Throat, Ann. Surg. **84**:456-459, 1926.

15. Ludwig, W., and Jarisch, A.: Ueber die Wirkung des N. depressor mit besonderer Berücksichtigung der Beteiligung des Herzens, Arch. f. exper. Path. u. Pharmakol. **114**:240-251, 1926.

16. Hering, H. E.: Die Karotissinusreflexe auf Herz und Gefässe vom normal-physiologischen, pathologisch-physiologischen und klinischen Standpunkt. Gleichzeitig über die Bedeutung der Blutdruckzügler für den normalen und abnormen Kreislauf, Dresden, Theodor Steinkopff, 1927.

17. Koch, E., and Mies, H.: Chronischer arterieller Hochdruck durch experimentelle Dauerausschaltung der Blutdruckzügler, Krankheitsforschung **7**:241-256, 1929.

18. (*a*) Heymans, C.: Les fonctions réflexogènes de l'aorte et du sinus carotidien, Compt. rend. Soc. de biol. **107**:1293-1330, 1931; (*b*) Some Aspects of Blood Pressure Regulation and Experimental Arterial Hypertension, Surgery **4**:487-501, 1938.

19. Nowak, S. J. G., and Walker, I. J.: Experimental Studies Concerning Nature of Hypertension: Their Bearing on Surgical Treatment, New England J. Med. **220**:269-274, 1939.

20. Green, M. F.; DeGroat, A. F., and McDonald, C. H.: Observations on Denervation of the Carotid Sinuses and Section of the Depressor Nerves as a Method of Producing Arterial Hypertension, Am. J. Physiol. **110**:513-520, 1935.

21. Heymans, C., and Bouckaert, J. J.: Observations chez le chien en hypertension artérielle chronique et expérimentale, Compt. rend. Soc. de biol. **106**:471-473, 1931.

22. Ask-Upmark, E.: The Carotid Sinus and the Cerebral Circulation: Anatomical, Experimental, and Clinical Investigation, Including Some Observations on the Rete Mirabile Caroticum, Acta psychiat. et neurol., 1935, supp. 6, pp. 1-374.

cases. In 4 of the 5 cases reported by Bucy, a rise in blood pressure persisted for six to fourteen days. Ray and Stewart [12d] likewise observed a temporary rise in blood pressure in 4 cases after unilateral intracranial division of the glossopharyngeal nerve.

Bilateral denervation of the carotid sinus in man has been reported in the European literature by Lauwers,[23] Danielopolu [24] and Leriche, Fontaine and Froehlich.[25] These investigators reported no serious after-effects or any significant permanent changes in blood pressure. In this country the late effects of bilateral denervation of the carotid sinus in man, particularly the vascular reflexes, were studied in 2 cases by Capps and de Takáts.[26] They found that bilateral denervation of the carotid sinus in man failed to produce a permanent elevation of blood pressure and could result in postural hypotension, as shown in their 2 cases. The postural hypotension was explained as being due to a relatively lower sensitivity of the aortic depressor mechanism than that of the carotid sinus.

The literature reveals no case of bilateral intracranial division of the glossopharyngeal nerve in man. The present case is therefore reported because of its significance in the study of the vascular reflexes and because of the value of the procedure in the relief of pain in the throat radiating to both ears due to a malignant growth in the nasopharyngeal region.

## REPORT OF CASE

*History.*—Mr. J. T., aged 51, was admitted to the service of Dr. W. E. Chamberlain at Temple University Hospital on Jan. 12, 1945, with a diagnosis of squamous cell carcinoma of the epipharynx. Prior to admission he had had a course of roentgen irradiation to both sides of the neck and implantation of radium into the epipharyngeal area. His chief complaint was a deep-seated pain in the throat, which radiated to both ears, being more pronounced on the right side. He also had a pain which began over the left mastoid process and radiated upward above the ear. Since the roentgen therapy he had had bilateral pain in the neck, presumably due to irradiation neuritis. There was trismus of the jaws, so that it was difficult for him to take any but liquid nourishment. The general physical and neurologic examination otherwise showed nothing significant. Pressure on the carotid sinus on either side failed to produce any appreciable slowing of the heart. The electrocardiogram was normal. In view of the bilateral cervical pain and the excruciating bilateral pain in the throat, it was decided to do a posterior cervical rhizotomy and bilateral intracranial section of the glossopharyngeal nerve. The patient was, accordingly, transferred to the neurosurgical service for operation.

*Operation* (Jan. 19, 1945).—High cervical laminectomy, with removal of the rim of the foramen magnum, was performed, using local anesthesia.

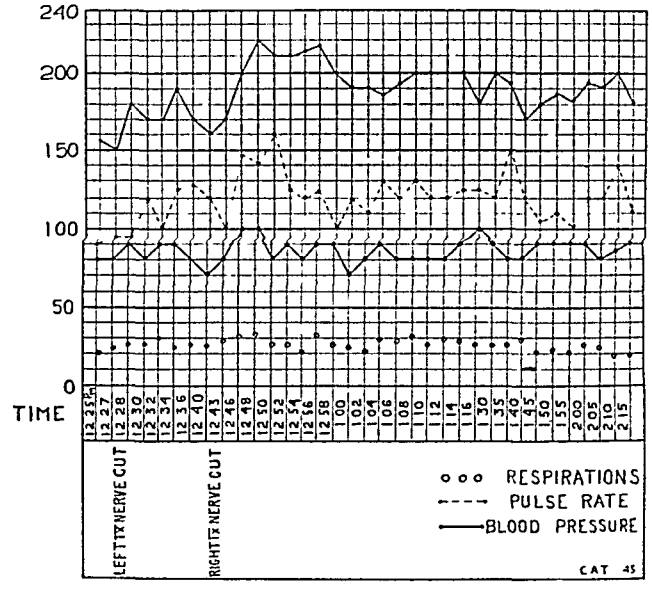



Fig. 1.—Observations on the pulse, respiration and blood pressure recorded by the anesthetist during operation. Note the immediate responses on section of each glossopharyngeal nerve.

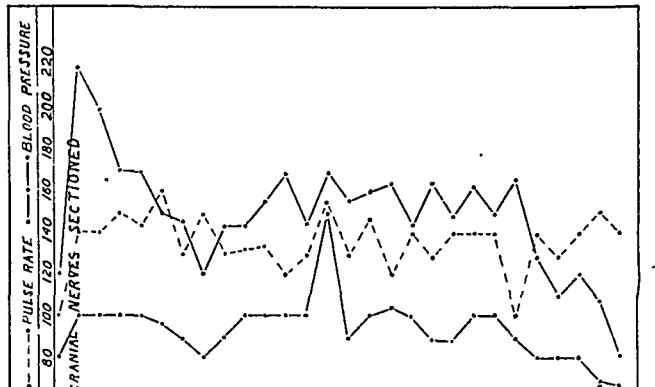



Fig. 2.—Observations on the pulse, respiration and blood pressure of the patient for a period of four weeks following operation. Note the persistent elevation of blood pressure except for five days prior to his death.

The laminas of the first to the fourth cervical vertebrae inclusive were removed. The posterior margin of the foramen magnum was rongeured away. The posterior roots of the first to the fourth cervical nerves inclusive were clipped and divided. With some difficulty, the cerebellum was retracted, exposing the ninth, tenth and eleventh cranial nerves on the left

23. Lauwers, E. E.: L'extirpation du corpuscule carotidien dans l'épilepsie, J. de chir. **37**:686-702, 1931.

24. Danielopolu, D.: Sur la pathogénie de l'épilepsie et sur son traitement chirurgical, Presse méd. **41**:170-174, 1933.

25. Leriche, R.; Fontaine, R., and Froehlich, F.: L'énervation sinu-carotidienne, Presse méd. **43**:1217-1220, 1935.

26. Capps, R. B., and de Takáts, G.: The Late Effects of Bilateral Carotid Sinus Denervation in Man: A Report of Two Cases with Studies of the Vascular Reflexes, J. Clin. Investigation **17**:385-389, 1938.

side. The preoperative blood pressure was 122 mm. of mercury systolic and 80 mm. diastolic. The pulse rate was 110 and the respiratory rate 20, per minute. Just prior to section of the left ninth nerve the record was as follows: pulse rate, 80 per minute; respiratory rate, 20 per minute, and blood pressure, 150 mm. systolic and 80 mm. diastolic. Immediately on section of the left ninth nerve, the pulse rate rose to 90 and the respiratory rate to 26, per minute; the blood pressure rose suddenly to 180 mm. systolic and 90 mm. diastolic (fig. 1). During the next fifteen minutes the blood pressure oscillated from 160 systolic and 70 diastolic to 190 systolic and 90 diastolic. At the end of fifteen minutes the right ninth nerve was cut. The response was immediate and dramatic. The pulse rate rose to 144 and the respiratory rate to 30, per minute. The blood pressure rose to 220 systolic and 100 diastolic (fig. 1). During the remainder of the operation the pulse rate varied from 100 to 160 per minute. The respiratory rate varied from 20 to 30 per minute. The blood pressure continued to be high and ranged from 190 systolic and 90 diastolic to 220 systolic and 100 diastolic (fig. 1).

For two hours after the operation the blood pressure remained between 170 systolic and 98 diastolic and 198 systolic and 100 diastolic and then fell to 160 systolic and 40 diastolic. During the next three days the blood pressure varied from 140 systolic and 80 diastolic to 168 systolic and 105 diastolic. The pulse ranged from 130 to 160 beats per minute and the respiratory rate from 20 to 36 per minute (fig. 2). The hypertension continued for four weeks, and the blood pressure did not reach preoperative levels until five days prior to the patient's death, when he showed signs of failing circulation (fig. 2).

Immediately after operation there was no dysphagia, and the patient could swallow liquids without choking. It was difficult to open his jaws because of the trismus, but it was noted that the gag reflex was absent bilaterally and that there was loss of sensation to pin prick and deep pressure over the posterior pharyngeal wall. The patient had definite sensation to pain in both auditory canals and over both tympanic membranes. There was sensory loss to all modalities over an area corresponding to the distribution of the upper four cervical dermatomeres. The patient was completely free of all pain. Unfortunately, bronchopneumonia and aspiration atelectasis developed. Bronchoscopic aspirations had to be done on several occasions. Dr. Charles Norris, who did the aspirations, noted free movement of both vocal cords. The sloughing mass in the epipharynx continued to feed the lungs below, and the patient finally died of suppurative pneumonitis, one month after operation.

*Autopsy* (February 15).—The brain was removed without disturbing the brain stem. The brain stem was carefully retracted, exposing the operative sites, where the ninth nerves had been cut (fig. 3). A small neoplasm, about the size of a cherry, was found projecting into the tip of the petrous portion of the right temporal bone. The surrounding area was a great mass of slough, which was due to irradiation necrosis. The lungs showed suppurative pneumonitis. The kidneys revealed cloudy swelling but no significant hypertensive changes.

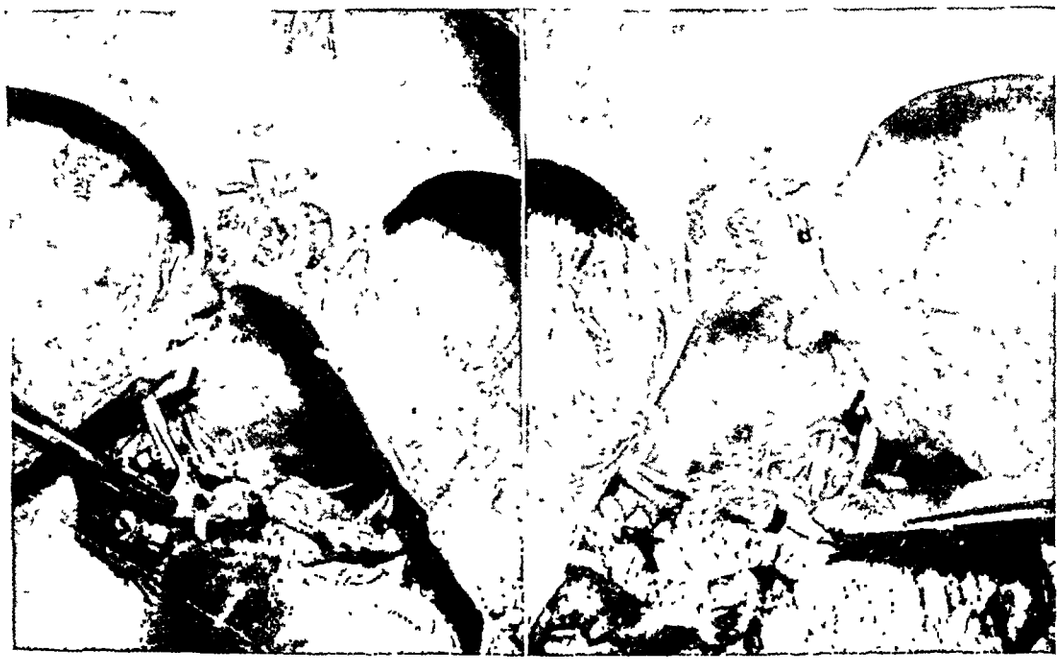


Fig. 3.—Autopsy specimen, showing the position of the sectioned glossopharyngeal nerve on the right and left sides. The arrows point to the divided nerve ends.

## COMMENT

A case is presented for the first time in which both ninth nerves were sectioned intracranially. The response of the blood pressure was immediate and dramatic and persisted until the patient's death, four weeks later. Pain in the throat with radiation to both ears is extremely distressing and cannot be relieved by unilateral section of the ninth nerve. The patient in this case was completely relieved of pain after bilateral section of this nerve. Bilateral section of the ninth nerve leaves the patient with an anesthetic pharynx and absence of the gag reflex. This condition should be compatible with life, provided the patient does not have a sloughing epipharyngeal mass which feeds the trachea below.

Temple University Hospital.

# MULTIPLE SCLEROSIS WITH LATE ONSET OF SYMPTOMS

ARNOLD P. FRIEDMAN, M.D.
AND
CHARLES DAVISON, M.D.
NEW YORK

The onset of symptoms in multiple sclerosis usually occurs between the second and the fourth decade of life. Its diagnosis, with few exceptions, is rarely entertained when signs of involvement of the central nervous system make their appearance in the fifth or the sixth decade of life. Wilson,[1] in a series of 1,107 cases of multiple sclerosis, found onset of symptoms after the age of 40 in 186, or 17 per cent, while von Hoesslin [2] found onset after the age of 50 in only 4 per cent. In many of the aforementioned cases the diagnosis was not verified by autopsy. Isolated examples of a very late onset with autopsy include Nielsen's [3] case, in which illness began in the late sixties, and Taga's [4] cases, in which the disease began after the age of 60.

In a series of 310 patients with multiple sclerosis who had been admitted to the Montefiore Hospital since 1922, the onset of symptoms after the age of 40 occurred in 41, or 13 per cent. Of the 42 patients on whom autopsy was performed, 9 (21 per cent) had the onset of symptoms after the age of 40. Because of the late onset, the diagnosis of multiple sclerosis was made before death for only 2 of the 9 patients. The case histories of these 9 patients have been studied in order to determine whether the symptoms and clinical course of the patients with a late onset of symptoms differs from that of patients with an onset early in life. The results are presented in the hope that they will be of value in establishing the diagnosis in other patients with late onset of symptoms.

From the Division of Neuropsychiatry, Montefiore Hospital, and the Department of Neurology, Columbia University College of Physicians and Surgeons.

1. Wilson, S. A. K.: Neurology, edited by A. N. Bruce, Baltimore, Williams & Wilkins Company, 1940.

2. von Hoesslin, R.: Ueber multiple Sklerose: Exogene Aetiologie, Pathogenese und Verlauf, Munich, J. F. Lehmann, 1934.

3. Nielsen, J. M.: A Textbook of Clinical Neurology, New York, Paul B. Hoeber, Inc., 1940.

4. Taga, K.: Zur Kenntnis der senilen multiplen Sklerose, Arb. a. d. neurol. Inst. a d. Wien. Univ. **31**: 163, 1929.

## REPORT OF CASES

CASE 1.—*Onset of symptoms referable to the brain stem and spinal cord at age of 53. Diagnosis of cervical neoplasm. Death following laminectomy two months after onset of symptoms.*

*History.*— R. M., a woman aged 53, was admitted to the Montefiore Hospital on June 8, 1937, with a history of numbness and weakness of the right upper extremity for two months. Soon after the onset of this symptom there appeared pain over the left side of the face, frontal headache and disturbance of vision in the left eye. A diagnosis of paranasal infection was made, and the symptoms disappeared after therapy. Weakness of both lower extremities and numbness of the left hand appeared. Her past illnesses included meningitis, in 1918, with residual deafness in the right ear, and arthritis of the lumbosacral region.

*Examination.*—The optic disks were normal. There were a Horner syndrome on the right, paralysis of the right upper and lower extremities and paresis of the left extremities. All deep reflexes were hypoactive and equal in the upper extremities. Ankle clonus and a Babinski reflex were elicited on the right side. The abdominal reflexes were absent. There was loss of pain and temperature sensation on the left side below the level of the third cervical dermatome.

*Laboratory Data.*—Examination of the blood and urine revealed nothing abnormal. The cerebrospinal fluid was under a pressure of 50 mm. of water. There was a prompt rise in pressure on jugular compression, but the fall in pressure was slow. These results were interpreted as indicating partial subarachnoid block. The fluid was clear and contained 7 lymphocytes per cubic millimeter and 66 mg. of protein per hundred cubic centimeters. A pronounced degree of spondylitis in the bodies of the cervical and thoracic vertebrae was shown roentgenographically.

*Course.*—On the basis of a presumptive diagnosis of tumor of the spinal cord, a laminectomy was performed under local anesthesia five days after the patient's admission. The cord was swollen, but no neoplasm was found. The postoperative course was stormy, and the patient died two days after operation.

*Report of Autopsy.*—A demyelinated plaque in the left occipital lobe destroyed part of the optic radiation and the white matter of the precuneus (fig. 1 *A*). The myelin sheaths in this area showed all types of destruction. In the cresyl violet preparations the plaque was filled with numerous compound granular corpuscles, microglia cells and occasional gemästete glia cells. Perivascular collections of lymphocytes, plasma cells, endothelial cells and compound granular corpuscles were in abundance. Proliferation of the vessels was noted in places. The proliferated vessels showed thickening of all coats.

An occasional hyalinized vessel was also noted. In the Holzer preparations there was extensive gliosis in the area with loss in myelin. In the Bielschowsky preparation, the axis-cylinders showed slight destructive changes, such as swelling, breaking down and a cork-screw appearance. Another plaque was found in the region of the cerebellar nuclei.

The segments of the cervical portion of the cord were enlarged and contained a large demyelinated plaque, which destroyed the greater part of the cord (fig. 1 *B*). In one segment of the cervical region hardly any white fibers were left. In the other sections some of the white fibers at the periphery of the cord were spared. There was no descending or ascending demyelination.

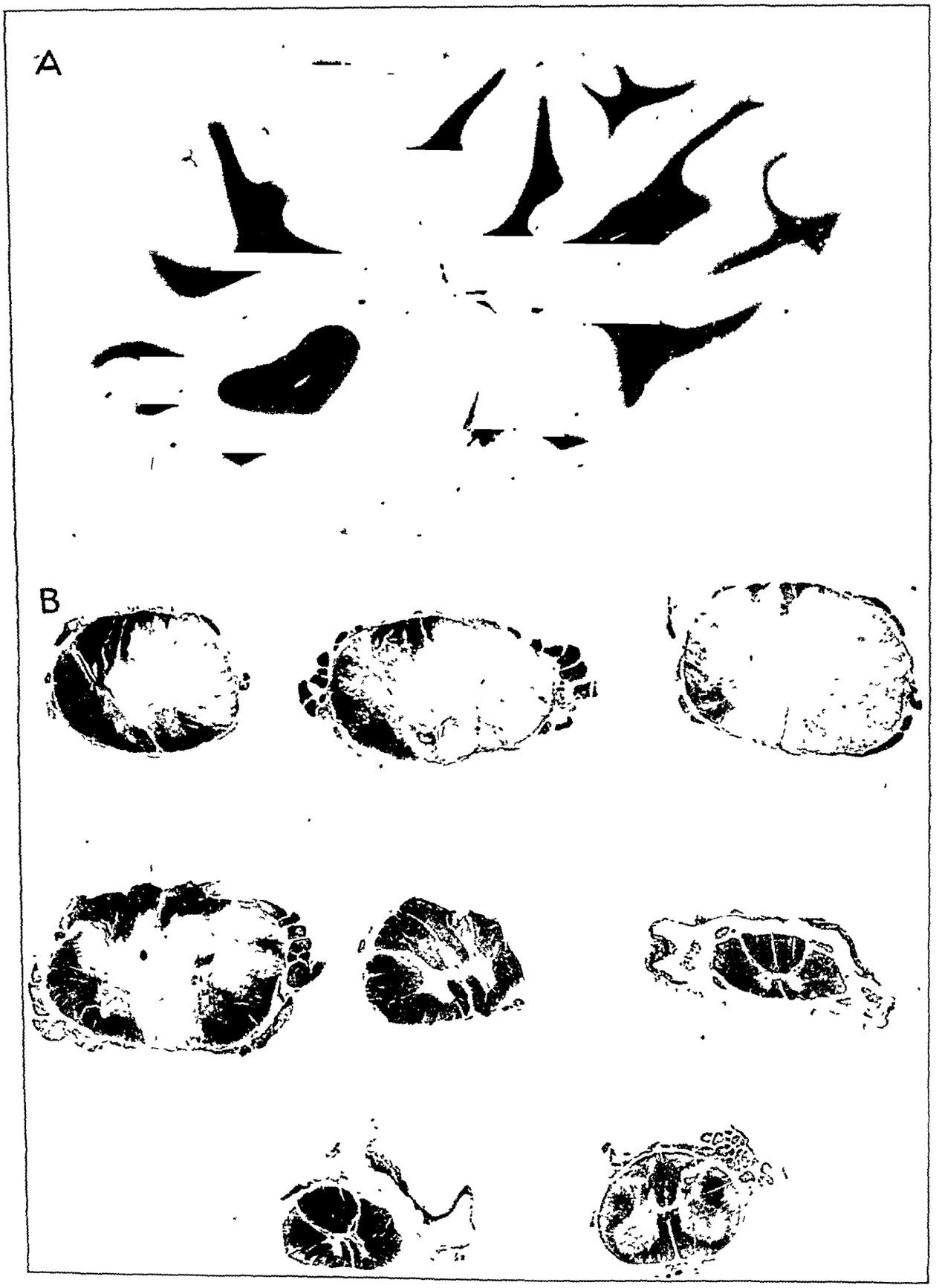



Fig. 1 (case 1).—Demyelinated area in the region of the optic radiation and white matter of the precuneus (*A*) and extensive plaque involving the cervical and upper thoracic regions (*B*). Notice that the middle lower thoracic and lumbar segments were spared. Myelin sheath stain.

The microscopic picture was the same as that of the area in the occipital convolutions. In the Bielschowsky preparations, the axis-cylinders were fairly well preserved, but in places they were swollen and had a corkscrew appearance and bulbous processes. The ganglion cells were well preserved, but in some areas a few showed shrinkage and chromatolysis or appeared as shadow cells. Complete destruction of ganglion cells was also noted.

*Comment.*—Because of the patient's age, the sudden onset and rapid progression of symptoms, essentially limited to the cervical portion of the cord, and the partial subarachnoid block, a diagnosis of neoplasm of the spinal cord was made. Histologically the lesions were typical of multiple sclerosis.

CASE 2.—*Onset of symptoms referable to the cerebellum and brain stem at age of 42. Progressive course, of fourteen years' duration.*

*History.*—L. S., a man aged 47, entered the Montefiore Hospital on Oct. 25, 1914, with a history of bouts of dizziness since 1909, followed a year later by transient diplopia. In 1911 there developed staggering gait and tremor of the hands. One year before his admission he became incontinent of urine.

*Examination.*—The pupils were miotic and responded to light but reacted sluggishly in accommodation. There were horizontal and vertical nystagmus, weakness of the right lower part of the face and marked tremor of the head and of all extremities on volitional movement. The reflexes were hypoactive; the abdominal reflexes were absent, and a Babinski sign was elicited on the right. Sensation was intact. There was incontinence of urine.

*Laboratory Data.*—Studies of the blood and spinal fluid, including Wassermann tests, revealed nothing abnormal. The urine was normal.

*Course.*—Throughout his stay in the hospital there was gradual progression of all symptoms. Eight years after his admission gastric distress developed and he had bouts of abdominal pain and vomiting. A diagnosis of peptic ulcer was made. Neurologic examination at this time showed scanning speech, hyperactive reflexes throughout and a bilateral Babinski sign. After fourteen years in the hospital the patient died suddenly of a ruptured peptic ulcer.

*Report of Autopsy.*—There was extreme internal hydrocephalus. Numerous well demarcated demyelinated areas, measuring from a few millimeters to 1 cm. in diameter (fig. 2), were scattered through both hemispheres. These foci of demyelination were present throughout the corona radiata, the thalamus and the temporal lobe. In the medulla oblongata there was a large area of demyelination near the fourth ventricle. The histologic appearance of these plaques was typical of multiple sclerosis. Study of the spinal cord disclosed neither secondary nor primary foci of demyelination.

*Comment.*—This case offered no diagnostic difficulties, and multiple sclerosis was considered by all observers to be the most probable diagnosis.

CASE 3.—*Onset of symptoms referable to the brain stem and spinal cord at age of 41. One remission of symptoms in an otherwise progressive course of twenty years' duration.*

*History.*—F. F., a woman aged 58, was admitted to the Montefiore Hospital on July 19, 1923, with a history of diplopia and bouts of dizziness since 1906. There was a remission of symptoms for one year. In 1908 there developed weakness, followed by complete paralysis. In 1917 she began to have pains and weakness in the right upper extremity.

*Examination.*—The pupils were equal and reacted to light and in accommodation. There were ptosis of the right upper lid, paralysis of the left external rectus muscle, paresis of the right external rectus muscle, horizontal and vertical nystagmus, weakness of the lower right side of the face, atrophy of the left side of the tongue, dysarthria, flaccid paralysis of the right arm and leg, spastic paralysis of the left leg and atrophy of the muscles of both lower extremities. The deep reflexes were hypoactive and unequal. Abdominal reflexes were absent. A Babinski sign was present bilaterally. There was impairment of all modalities of sensation on the right side of the body. The mental status was normal.

*Laboratory Data.*—There was a faint trace of albumin in the urine. The cerebrospinal fluid was normal.

*Course.*—Shortly after admission the patient complained of difficulty in breathing and of hoarseness. This condition cleared up, but eight months later she experienced severe persistent pain on the right side of the jaw. Bronchopneumonia developed and she died thirty-nine months after entering the hospital, and approximately twenty years after the onset of the first symptom.

*Report of Autopsy.*—Typical, well demarcated demyelinated plaques were present in the white matter of the right first frontal convolution, the right centrum ovale, the insular and temporal convolutions, the right neostriatum bordering the external capsule, the fornix, the lateral and medial nuclei of the right thalamus, the gray and white matter of the postcentral convolutions, the right insula, the right hippocampus, the temporal lobes and the optic radiations (fig. 3). In sections through the brain stem and cerebellum the entire upper part of the tegmentum was replaced by a plaque. The myelin sheaths and axis-cylinders in the center of most of the plaques had completely disappeared; those at the periphery were swollen and fragmented. In the cresyl violet preparation the plaques were filled with rod-shaped microglia cells and astrocytes. At the periphery there were numerous gemästete glia cells. Occasional perivascular infiltrations, consisting of nuclei of compound granular corpuscles, were noted.

Demyelinated plaques were present in various regions of the spinal cord and involved the gray matter, the crossed and direct pyramidal tracts, the posterior columns and the ventral cerebellar, rubrospinal and spinothalamic pathways. Many of the nerve cells in the gray matter had been destroyed, and many of the remaining cells had undergone various pathologic changes, ranging from almost complete disappearance of the ganglion cells to neuronophagia, satellitosis or loss of Nissl substance. The anterolateral and anteromesial groups were more involved than the dorsolateral and dorsomesial groups.

*Comment.*—Although paralysis of ocular nerves and atrophy of the muscles of the tongue and the extremities are rare in cases of multiple sclerosis, the diagnosis of this disease was entertained by several of the examiners. One of us

Fig. 2 (case 2).—Numerous demyelinated plaques scattered throughout the white matter. Myelin sheath stain.

Fig. 3 (case 3).—Section through the temporal horn, showing demyelinated areas throughout the white matter, especially in the vicinity of the ventricle. Notice the small plaque in the hippocampus. Myelin sheath stain.

(Davison) and associates [5] previously reported a series of cases of multiple sclerosis with changes in the anterior horn cell and atrophy of muscles.

CASE 4.—*Onset at age of 43 with signs of involvement of the cerebellar and pyramidal tracts. Progressive course, with death after fifteen years.*

*History.*—J. M., a man aged 54, a house painter, who was admitted to the Montefiore Hospital on July 5, 1935, had onset of periodic pain and cramps in his calves in 1923. About six months later he experienced weakness and unsteadiness of his legs, which progressed so that he was unable to walk without the use of a cane. In 1935 there appeared urgency in micturition, followed by weakness and unsteadiness of the upper extremities. About six months before his admission his handwriting became totally illegible.

*Examination.*—The pupils were irregular in outline but reacted well to light and in accommodation. There were horizontal nystagmus and hoarseness of the voice, and the gag reflex was absent. Muscular power was diminished in all extremities. The deep reflexes were active throughout. The abdominal reflexes were present, and there was a questionable Babinski sign on the right side. The gait had a wide base, and ataxia was present in all extremities but was more marked on the right side. The sensory examination was normal. There were evidences of intellectual deterioration.

*Laboratory Data.*—Studies of the blood and cerebrospinal fluid, including the Wassermann tests, gave normal results except for a protein content of the cerebrospinal fluid of 58 mg. per hundred cubic centimeters. The urine was normal.

*Course.*—The condition of the patient did not change greatly during his three year stay in the hospital, although dissociation of ocular movements and dysarthria were recorded by several observers. Coronary occlusion developed, and the patient died on July 17, 1938, fifteen years after the onset of the neurologic signs.

*Report of Autopsy.*—There were numerous discrete areas of demyelination throughout the white matter of the cerebral convolutions, in the right insula, the corpus callosum, the right internal capsule, the right pulvinar and the right substantia nigra, around the aqueduct of Sylvius (fig. 4 *A* and *B*), and in the left brachium conjunctivum, the left pyramid, the right dentate nucleus, the corpus restiforme, the right medial lemniscus and the cerebellum. In the spinal cord there was a plaque in the posterior columns. The microscopic changes of the myelin sheaths, axis cylinders and glia cells were typical of multiple sclerosis. Many of the ganglion cells in the plaques which extended into the gray matter were well preserved; some, however, appeared as shadow cells. Occasional destruction of the ganglion cells was also noted.

There were thickening of the intima, splitting of the lamina elastica and fenestration and thinning of the other muscular coats of the right middle cerebral and left vertebral arteries.

*Comment.*—Because of the pronounced cerebellar signs and dysarthria, the diagnosis during life was olivopontocerebellar atrophy. The signs referable to the pyramidal tract were not considered to be significant by most of the examiners. Pathologically the lesions were typical of multiple sclerosis. Although there was evidence of arteriosclerosis in some of the cerebral vessels, there were no areas of softening. The atherosclerotic process occurred shortly before death.

CASE 5.—*Onset of cerebral symptoms at age of 64. Death from uremia one year after onset of symptoms.*

*History.*—S. P., a man aged 65, was admitted to the Montefiore Hospital on Dec. 22, 1932, with a history of frequent and painful urination since April 1931. A tentative diagnosis of nephrolithiasis was made. One year later he returned complaining of hematuria and pain in the perineum. A diagnosis of carcinoma of the bladder was made, and he received eight roentgen ray treatments. Personality changes and loss of memory had been noted for one year.

*Examination.*—The pupils reacted sluggishly to light and in accommodation. There were horizontal nystagmus, slight intention tremor bilaterally in the finger to nose test and hyperactive deep reflexes throughout. The patient's mood was labile and irritable. Speech was incoherent and irrelevant. He was poorly oriented, and memory for recent events was poor. Insight and judgment were defective. The blood pressure was 130 systolic and 70 diastolic. The prostate was enlarged and indurated.

*Laboratory Data.*—The urine was loaded with pus cells, and gave a 1 plus reaction for albumin. There was moderately severe hypochromic anemia. Roentgenograms of the pelvis and the spine revealed no evidence of metastasis. Wassermann reactions of the blood and the spinal fluid were negative. Examination of the cerebrospinal fluid revealed nothing remarkable. Cystoscopic examination showed a neoplasm of the bladder.

*Course.*—Two months after admission the patient became torpid and finally stuporous, in which condition he remained until his death, four days later, with uremia.

*Report of Autopsy.*—Autopsy showed a carcinoma of the bladder with metastases to the lungs and pelvic and tracheobronchial lymph nodes.

*Central Nervous System.*—The frontal convolutions were greatly atrophied. The anterior horns of the lateral ventricles were extensively dilated. There was pronounced atrophy of the white matter. The striatum, especially the caudate nucleus, was shrunken. Demyelinated plaques were present in the corona radiata of both hemispheres, in the optic radiations and in the right substantia nigra (fig. 5). Histologically the plaques were typical of multiple sclerosis.

*Comment.*—Because of the patient's age, the late onset of symptoms and the absence of remissions, the neurologic signs were attributed to cerebral arteriosclerosis. At autopsy the central nervous system disclosed a typical picture of multiple sclerosis.

CASE 6.—*Onset of symptoms referable to the spinal cord at age of 41. Progressive course, of eleven years' duration.*

*History.*—A. B., a man aged 50, was admitted to the Montefiore Hospital on Dec. 1, 1931, with a history of staggering gait, intermittent cramplike pains in the legs and weakness of the legs, which began in 1922 and pro-

5. Davison, C.; Goodhart, S. P., and Lander, J.: Multiple Sclerosis and Amyotrophies, Arch. Neurol. & Psychiat. **31**:270 (Feb.) 1934.

gressed until he was unable to walk without the aid of crutches. In 1926 there appeared urgency of urination, with occasional incontinence. A year later the first episode of incontinence of feces occurred, and on his admission there was total incontinence of both urine and feces. Loss of power of erection occurred in 1927. In May 1931 a laminectomy was performed at another hospital, but no neoplasm was found and the patient was discharged with the diagnosis of adhesive arachnoiditis.

*Examination.*—There were horizontal and vertical nystagmus, a left Horner syndrome, spastic paraplegia, hyperactive reflexes in all extremities, bilateral ankle clonus, absence of abdominal reflexes, a bilateral Babinski sign, impaired vibration and position sensations in the lower extremities and total incontinence of urine and feces.

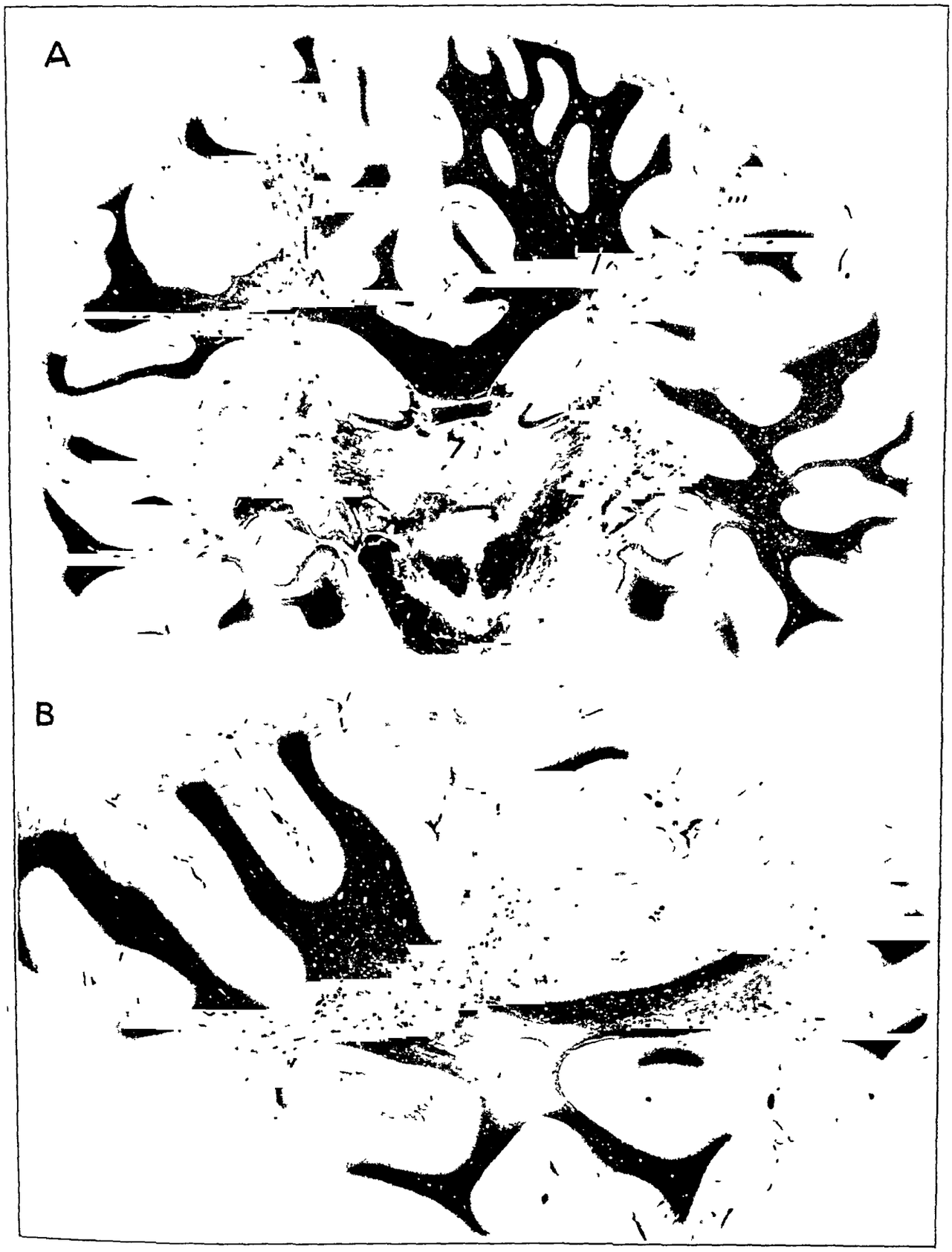



Fig. 4 (case 4).—Areas of demyelination in the white matter of the temporal and hippocampal convolutions, in the thalamic nuclei, about the aqueduct of Sylvius and in the substantia nigra (*A*), as well as in the white matter around the posterior horn of the lateral ventricle and the white matter of the occipital convolutions (*B*). Myelin sheath stains.

*Laboratory Data.*—Examination of the blood and urine revealed nothing significant. The cerebrospinal

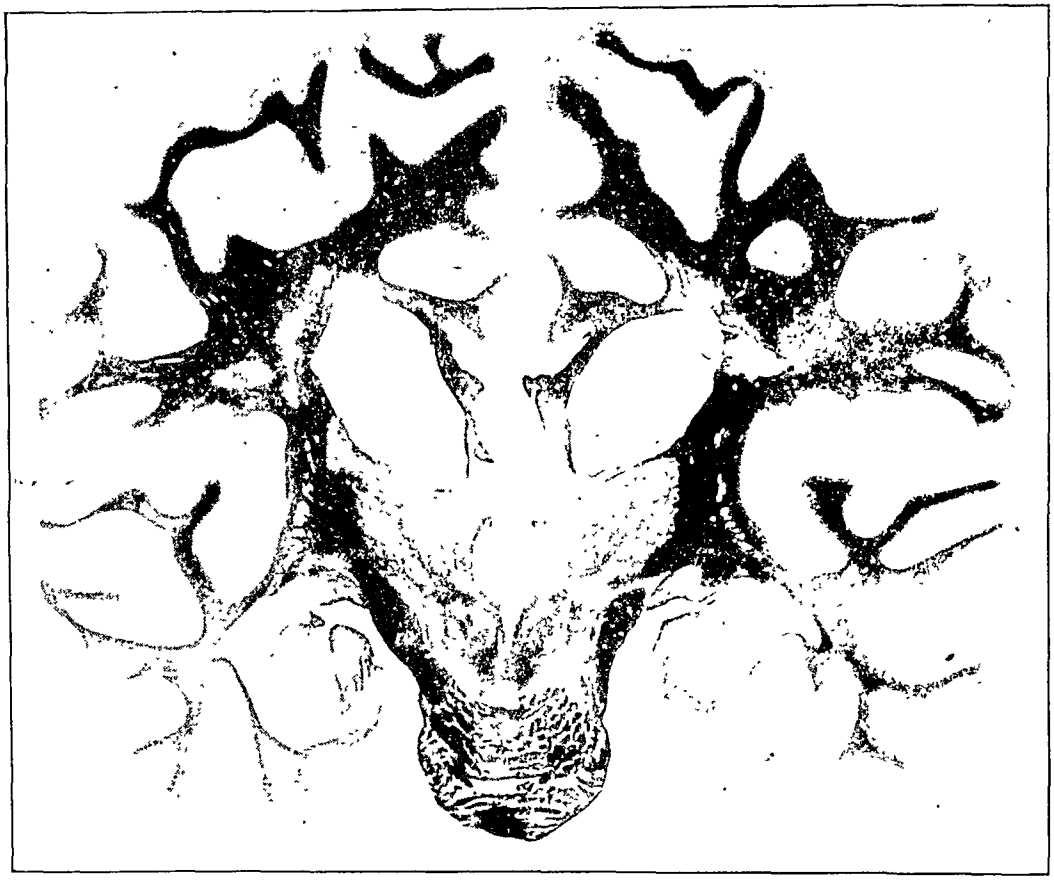


Fig. 5 (case 5).—Numerous demyelinated plaques in the white matter and the substantia nigra. Notice atrophy of the convolutions and internal hydrocephalus. Myelin sheath stain.

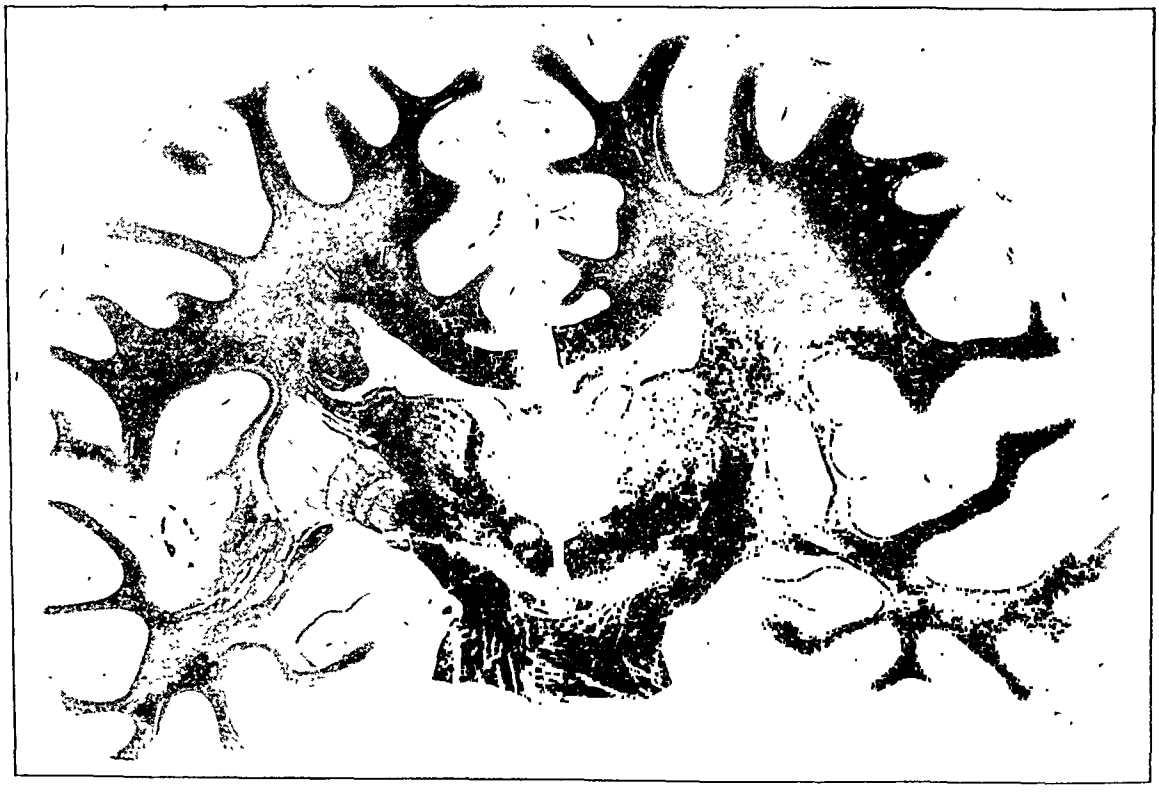


Fig. 6 (case 6).—Small demyelinated area near the ventricle, in the hypothalamus — best seen on the right—and in the insular fibers on the left. Myelin sheath stain.

fluid was under a pressure of 70 mm. of water, and the dynamics were normal. The fluid contained no cells. The protein content was normal; the Wassermann reaction was negative, and the mastic test gave a normal curve.

*Course.*—Several months after the patient's admission paraplegia in flexion developed. There were periods of marked euphoria. Bronchopneumonia developed, and the patient died in August 1933.

*Report of Autopsy.*—The frontal convolutions were slightly atrophied. Demyelinated plaques were present

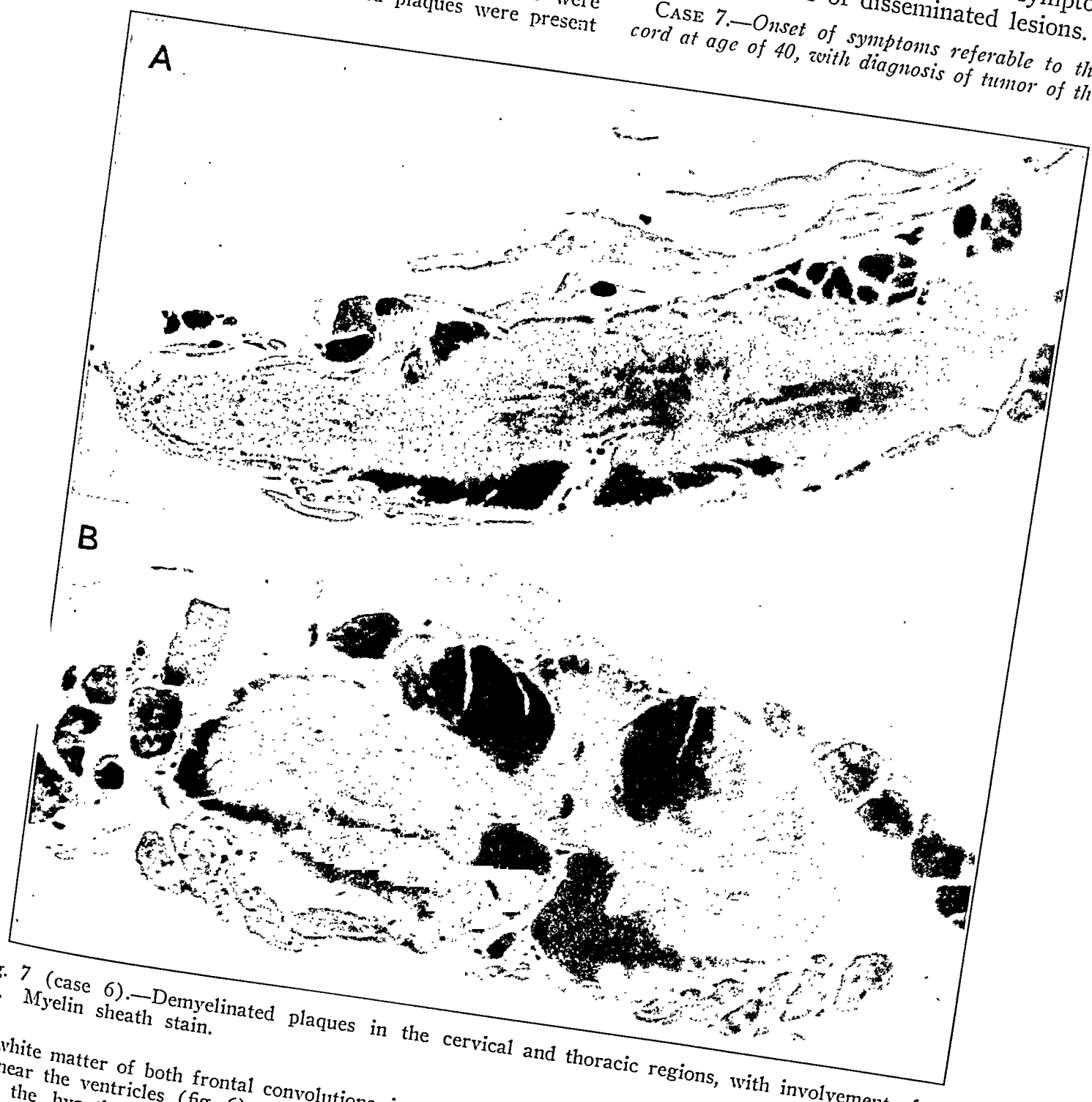



Fig. 7 (case 6).—Demyelinated plaques in the cervical and thoracic regions, with involvement of the gray matter. Myelin sheath stain.

in the white matter of both frontal convolutions, in the insula, near the ventricles (fig. 6), and in the internal capsule, the hypothalamus, the optic radiations, the dentate nuclei, the medulla oblongata and the spinal cord (fig. 7). The myelin sheaths and axis-cylinders showed the changes typical of multiple sclerosis. The hypothalamic region was densely infiltrated with glia cells, especially microglia cells. Some of the nerve cells had a shadow-like appearance, were completely destroyed or showed pigment atrophy. In the spinal cord some of the plaques also invaded the gray matter (fig. 7). The ganglion cells in these areas, although not destroyed, showed pathologic changes such as chromatolysis, pyknosis, pigment atrophy and occasional disintegration.

*Comment.*—Early in the course of the illness the diagnosis of a neoplasm of the spinal cord was made, and an exploratory laminectomy was performed. Later, however, the symptoms disclosed evidences of disseminated lesions.

CASE 7.—*Onset of symptoms referable to the spinal cord at age of 40, with diagnosis of tumor of the spinal cord and laminectomy. Progressive course of two years' duration.*

*History.*—M. S., a man aged 42, was admitted to the Montefiore Hospital on Aug. 8, 1942, with a history of numbness of the hands and generalized weakness since 1940. Shortly after the onset of these symptoms the muscles of the left hand became atrophied. In 1941 iodized poppyseed oil was injected intrathecally. After this, he had difficulty with his gait and complained of severe headaches. Progressive weakness of the lower extremities, difficulty in starting the urinary stream and constipation developed. Four months before his admission a spinal tap was done at another hospital. Within

a few hours after this the temperature rose, and he grew drowsy and became paralyzed from the waist down. Sensation was lost in the lower extremities, and occasionally painful flexor spasms occurred. The symptoms, a laminectomy was performed, but no tumor was found. On admission to the Montefiore Hospital the patient appeared wasted and malnourished. There were decubitus ulcers over the sacrum.

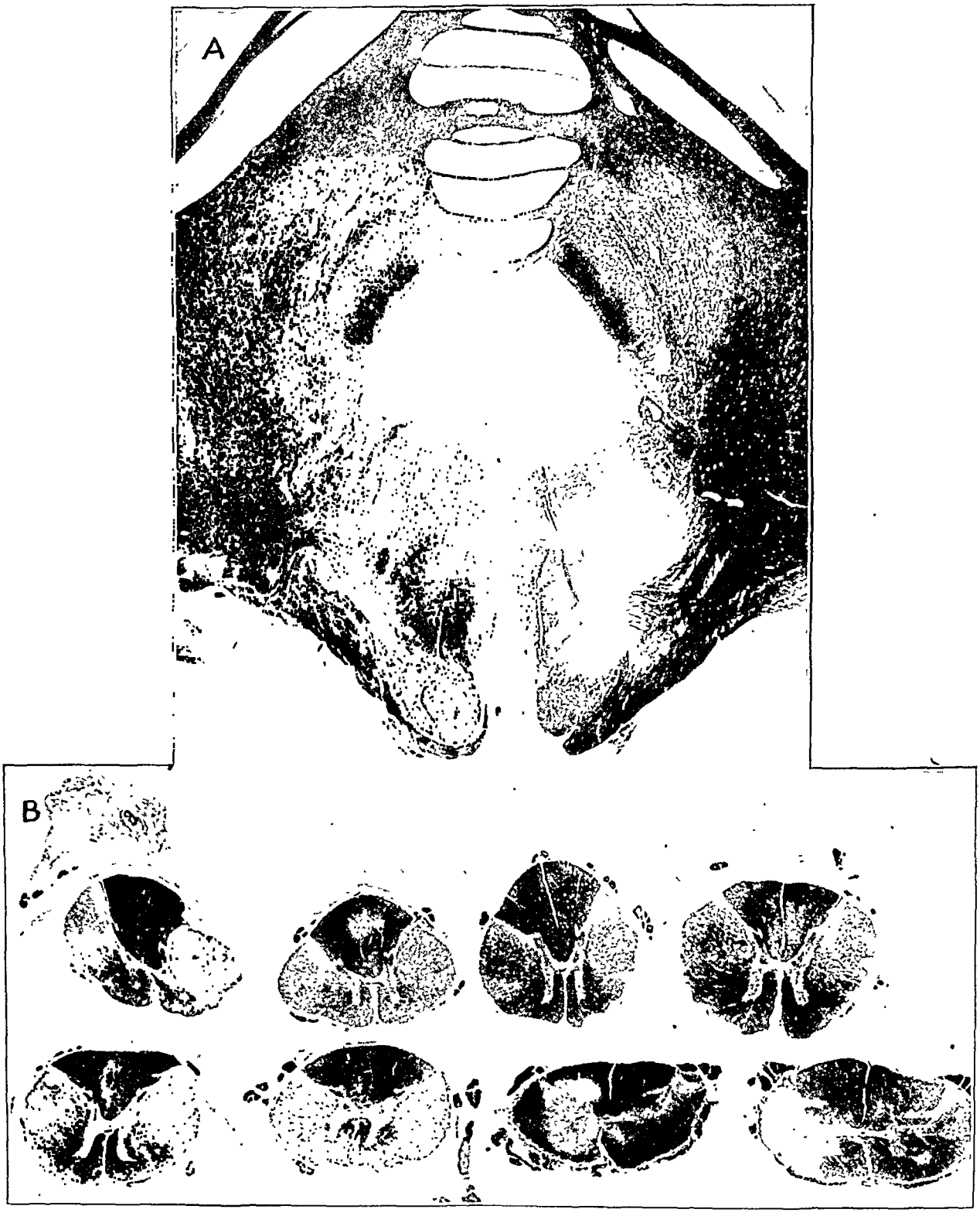



Fig. 8 (case 7).—Demyelinated plaque in the right portion of the brain stem, involving the nuclei of the sixth and the seventh cranial nerves, the trapezoid body, the superior olive, the thalamo-olivary tract, the medial lemniscus and the pyramid (*A*) and the area of demyelination in the ventrolateral tracts of the thoracic regions and a plaque in the lumbar enlargement (*B*). Myelin sheath stain.

fluid obtained at this puncture contained 12 lymphocytes per cubic millimeter and a total protein of 75 mg. per hundred cubic centimeters, but there was no evidence of spinal block. Because of the rapid progression of

*Examination.*—There were horizontal nystagmus, generalized wasting of the musculature, more marked in the distal parts of the arms, hyperactive refleves in the upper and absence of reflexes in the lower

extremities and absence of abdominal reflexes. Sensory examination was unsatisfactory because of the unreliability of the patient's responses.

*Laboratory Data.*—A lumbar puncture at this hospital was not done. Examination of the blood revealed severe secondary anemia.

*Course.*—The patient was febrile and complained of sharp pain in both upper extremities. He died two weeks after entry to this hospital, after bronchopneumonia.

*Report of Autopsy.*—There were demyelinated plaques surrounding the superior part of the aqueduct of Sylvius and in the white matter about the dentate nucleus. In the brain stem, a demyelinated plaque involved the posterior longitudinal bundle, the nuclei of the fifth and sixth cranial nerves and the genu of the seventh nerve. In the same area, another large plaque involved parts of the trapezoid body, the superior olive, the thalamo-olivary tract, the medial lemniscus and the pyramid (fig. 8 *A*). Throughout the spinal cord were numerous plaques. The cord disclosed areas of demyelination in the venterolateral tracts and a plaque in the lumbar region (fig. 8 *B*). The anterior horn cells showed pathologic changes. The rest of the microscopic picture was typical of multiple sclerosis.

*Comment.*—Because of sensory changes and atrophy of muscles, the diagnosis of neoplasm of the spinal cord was made in this case, but no tumor was found at operation. At autopsy, the lesions observed were those of multiple sclerosis.

CASE 8.—*Onset of spinal and cerebral symptoms at age of 46. Progressive course of seven years' duration.*

*History.*—E. K., a woman aged 52, was admitted to the Montefiore Hospital on May 31, 1942, with a history of severe weakness of the legs in 1936, followed in 1938 by weakness in the arms. Since 1940 the patient had been bedridden. There were also emotional lability and impaired memory for recent events. Six months before her admission urinary incontinence developed.

*Examination.*—There were horizontal nystagmus, scanning speech, intention tremor, generalized weakness of all extremities, hyperactive reflexes throughout, absence of abdominal reflexes and a bilateral Babinski sign. Sensory modalities were impaired in a diffuse manner, but, because of her mental status, no definite evaluation was given the tests. The patient was euphoric. There were emotional lability, impairment of attention and marked loss of memory for recent events.

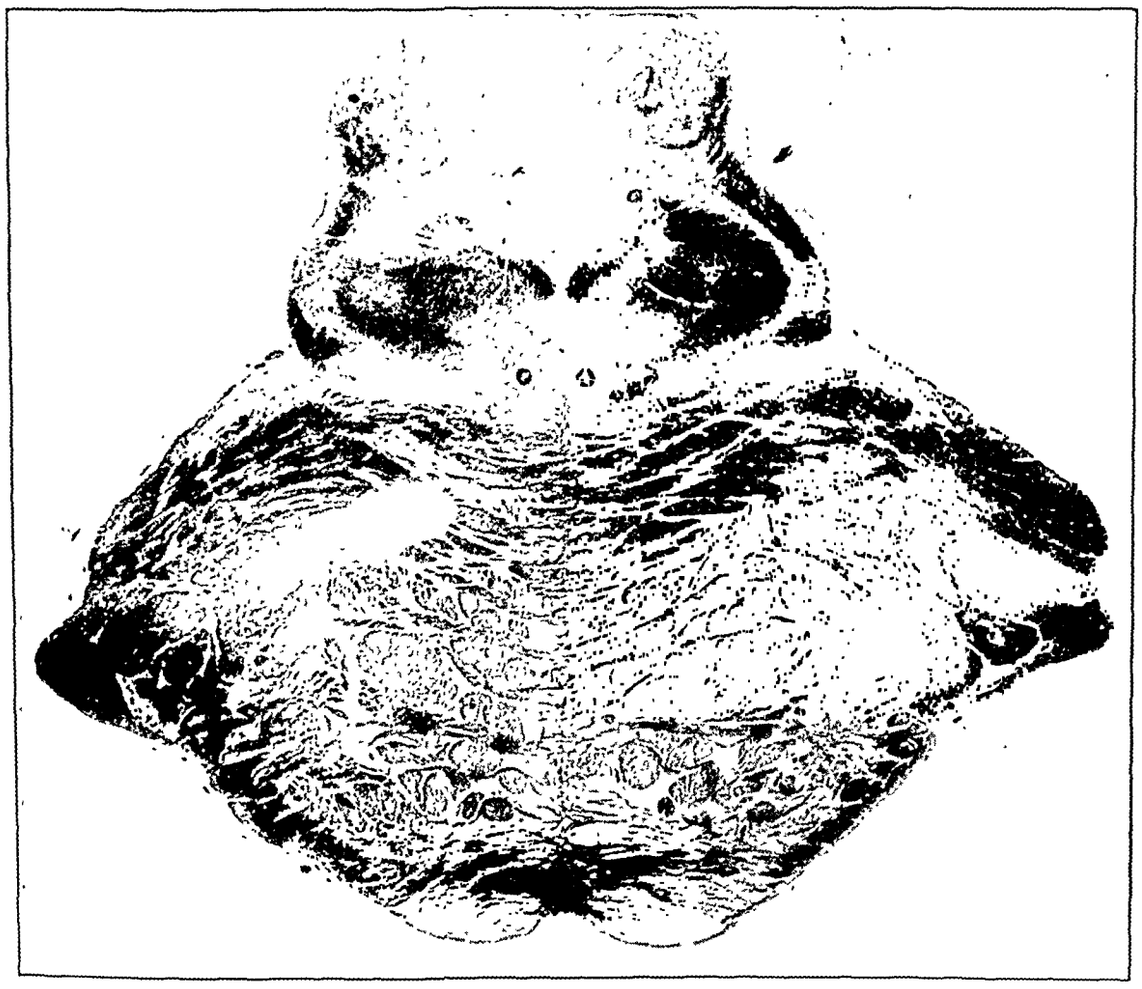


Fig. 9 (case 8).—Numerous demyelinated areas scattered throughout the pons. Myelin sheath stain.

*Laboratory Data.*—The blood and urine were normal. The Wassermann reactions of the blood and the cerebrospinal fluid were negative. The cerebrospinal fluid was normal except for the total protein content, which was 63 mg. per hundred cubic centimeters. Electroencephalogram and the air encephalogram were normal. A roentgenogram of the chest showed nothing abnormal.

*Course.*—During her stay in this hospital the patient's condition gradually deteriorated. One year after her admission there developed painless jaundice of obstructive type, due to carcinoma of the pancreas, and she died three weeks later of bronchopneumonia.

*Report of Autopsy.*—Demyelinated plaques were found in the white matter near the ventricles and in the optic radiations, pons (fig. 9) and medulla oblongata. These were typical of multiple sclerosis. Stains of the spinal cord for myelin sheaths revealed an area of

demyelination in the posterior columns. In the cresyl violet preparations the anterior horn cells, although normal, showed occasional slight pyknosis and shrinkage.

*Comment.*—Because of the late onset and the absence of remissions, many observers did not consider this case as one of multiple sclerosis.

CASE 9.—*Onset of symptoms of the brain stem and spinal cord at age of 43. One remission of symptoms in a course of fifteen years' duration.*

*History.*—C. F., a woman aged 51, was admitted to the Montefiore Hospital on Dec. 25, 1925, with a history of a transitory attack of blindness in the left eye in 1917, followed by numbness of the hands and difficulty in manipulating the fingers. In 1924 there developed weakness of both lower extremities and urinary incontinence.

She had had influenza in 1918 and an appendectomy in 1921. Arterial hypertension was first noted in 1923.

*Examination.*—The left pupil was larger than the right but reacted to light and in accommodation. There were pallor of the left optic disk and weakness of the lower right part of the face. The reflexes were hyperactive but equal on the two sides; the abdominal reflexes were absent. The Babinski sign was present bilaterally. Vibration sense was lost in all extremities. There was urinary incontinence. Mental examination revealed general complacency, with a tendency to euphoria. The heart was enlarged to the left, and the blood pressure was 170 systolic and 95 diastolic.

*Laboratory Data.*—The blood and urine were normal. The Wassermann reactions of the blood and the cerebrospinal fluid were negative. The cerebrospinal fluid was normal except for a protein content of 56 mg. per hundred cubic centimeters. Roentgenograms of the chest showed some enlargement of the left ventricle and dilatation of the aorta.

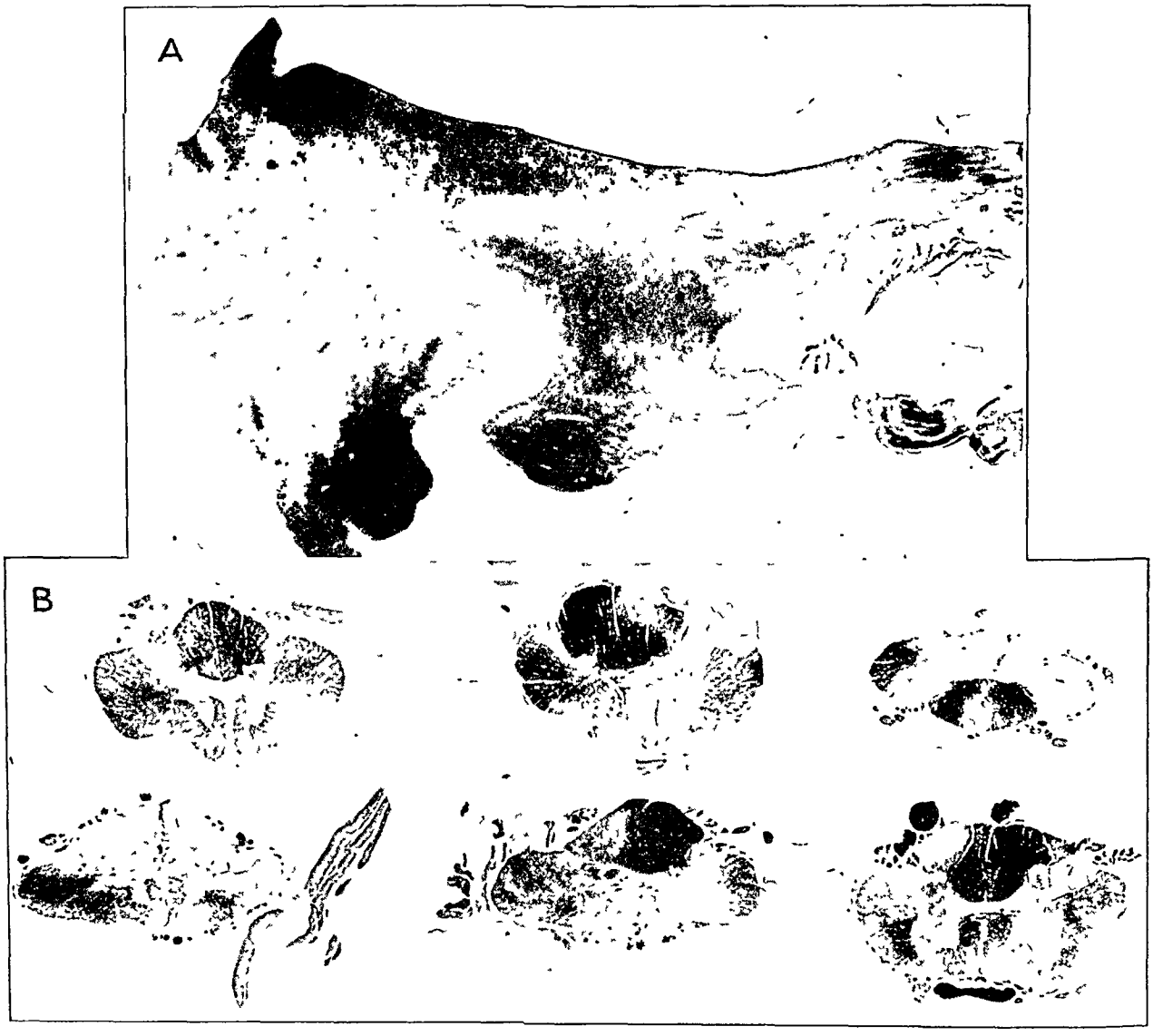



Fig. 10 (case 9).—Plaque in the region of the optic chiasm and tract (*A*) and numerous plaques scattered throughout the spinal cord (*B*). Myelin sheath stain.

*Course.*—Three months after admission the patient was unable to walk because of weakness of her legs. Examination at this time revealed a sensory level at the seventh dorsal segment. Another examination of the spinal fluid revealed nothing abnormal. In 1927 there appeared horizontal nystagmus, marked memory defect for recent events and emotional lability. In 1928 a diagnosis of diabetes mellitus was made on the results of a routine urinalysis, and the patient was treated with insulin. Weakness and atrophy of the upper extremities became severe. The mental condition deteriorated to the extent that she responded little to questioning, and

these responses were mostly incoherent and irrelevant. There developed severe anemia; she became febrile and had periods of stupor, interspersed with lucid intervals, and died of bronchopneumonia in 1932.

*Report of Autopsy.*—There was slight atrophy of the frontal convolutions. The vessels at the base of the brain showed atherosclerotic changes. The right optic nerve was shrunken. There were areas of softening in the right putamen. Plaques were not seen grossly. Sections of the optic nerve and chiasm disclosed demyelination of the nerves, tracts and chiasm (fig. 10 *A*). The myelin sheaths presented all types of pathologic changes, such as complete disappearance, swelling and slight disintegration. The axis-cylinders in the completely demyelinated areas were gone. In the cresyl violet preparations the demyelinated areas were filled with microglia cells, gemästete glia cells and some multinucleated giant cells.

Sections through the substantia nigra showed no visible plaques or areas of softening. A few of the perivascular spaces throughout the diencephalic region contained inflammatory cells. The nerve cells in these areas showed neuronophagia, satellitosis or complete destruction. Occasional glia nodules, consisting of inflammatory cells, microglia cells and a few gemästete glia cells, were also noted. In other regions there were large accumulations of glia nodules, consisting of microglia cells and compound granular corpuscles.

In sections through the basal ganglia, a small area of destruction was noted between the outer and the inner segment of the globus pallidus. This was a typical area of thrombotic softening. The pallidal vessels were calcified. There was also blood pigment engulfed by compound granular corpuscles and a few glia cells. Actual plaques were not seen. A few perivascular spaces contained lymphocytes, plasma and endothelial cells and microglia cells.

The middle cerebral artery and some of the other cerebral arteries were thickened, and there were proliferation of the intima, splitting of the lamina elastica, fenestration and deposits of cholesterol.

The entire spinal cord appeared thinner than normal. An area of softening was noted at about the level of the seventh and eighth dorsal segments. There was some apparent translucency of the posterior columns in the high cervical region. Areas of discrete demyelination were present throughout. In some regions practically the entire cord was involved (fig. 10 *B*). The myelin sheaths and axis-cylinders showed changes similar to those in the optic chiasm. In the sudan III preparations lipid deposits were found in the demyelinated plaques; these were more numerous at the border between the completely demyelinated plaques and healthy tissue. In the cresyl violet preparations the demyelinated areas and the gray matter in many sections were filled with numerous glia elements. Some of the nerve cells showed pyknosis or complete destruction.

*Comment.*—Clinically, this patient presented a picture of multiple sclerosis, which came on at the age of 43. The process essentially involved the optic tract and the spinal cord. Eight years after the original symptoms hypertension developed. Because of this, many observers believed the case to be one of vascular disorder of the central nervous system. At autopsy the cerebral vessels and the lesions in the pallidal segments showed changes typical of atherosclerosis. The lesions in the optic pathways and the spinal cord were, however, typical of multiple sclerosis.

*Analysis of Nine Cases of Multiple Sclerosis with Onset of Symptoms After the Age of 40*

| Case | Age at Onset, Yr. | Duration of Disease | Course | Cause of Death | Signs and Symptoms: Spinal: Tracts | Signs and Symptoms: Spinal: Ventral Horn Cells | Signs and Symptoms: Brain Stem: Tracts | Signs and Symptoms: Brain Stem: Nerves or Nuclei | Signs and Symptoms: Mental Symptoms | Associated Disease | Protein Content of Cerebrospinal Fluid |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 53 | 2 mo. | 1 remission | Postoperative complications | + | — | — | + | — | — | 66 mg./100 cc.; increased |
| 2 | 42 | 14 yr. | Progressive | Ruptured duodenal ulcer | — | — | + | + | — | Gastric ulcer | Normal |
| 3 | 41 | 20 yr. | 1 remission | Bronchopneumonia | + | + | + | + | — | — | Normal |
| 4 | 43 | 15 yr. | Progressive | Coronary thrombosis | + | — | + | + | + | Arteriosclerosis, cerebral | 58 mg./100 cc.; increased |
| 5 | 64 | 1 yr. | Progressive | Uremia | — | — | + | — | + | Carcinoma of bladder | Normal |
| 6 | 41 | 11 yr. | Progressive | Bronchopneumonia | + | — | + | — | + | — | Normal |
| 7 | 40 | 2 yr. | Progressive | Bronchopneumonia | + | + | — | — | + | — | 75 mg./100 cc.; increased |
| 8 | 46 | 7 yr. | Progressive | Bronchopneumonia | + | — | + | — | + | Carcinoma of pancreas | 63 mg./100 cc.; increased |
| 9 | 43 | 15 yr. | 1 remission | Bronchopneumonia | + | — | — | + | + | Diabetes mellitus; cerebral arteriosclerosis | 56 mg./100 cc.; increased |

## COMMENT

Multiple sclerosis is usually considered a disease of young adults, and the diagnosis is rarely considered in cases in which the initial symptoms occur in the fifth or the sixth decade of life. The incorrectness of such a point of view is clearly demonstrated by the present report. In 21 per cent of all cases at the Montefiore Hospital proved by autopsy to be instances of multiple sclerosis, the first symptoms appeared during or after the fifth decade of life (table). Wilson [1] and others have reported similar obser-

vations in series of cases clinically diagnosed as multiple sclerosis.

In our series there were 9 patients with late onset of symptoms (after the age of 40). All were Jewish [6] and brunette. Five were men and 4 were women. The duration of life after known onset of the disease was from two months to twenty years, with an average of over eight years. The cause of death, as in most cases of multiple sclerosis, was some intercurrent disease, which was bronchopneumonia in 5 patients. Of the other 4 patients the respective causes of death were uremia, coronary thrombosis, perforated duodenal ulcer and a complication following exploratory laminectomy.

The characteristic clinical course of multiple sclerosis is intermittent, with remissions and exacerbations, but occasionally the course may be progressively downhill, without any clear remissions. According to Birley and Dudgeon,[7] the remittent type occurred six times as frequently in all age groups as the chronic progressive type. In our series the clinical course was progressive in 6 patients and intermittent in 3 patients. Our data support the impression that in patients with the onset of symptoms in the fifth decade of life the disease more often has a chronic progressive course than in those whose first symptoms appear before this period.

The 3 patients whose course was intermittent had the following initial complaints: dizziness, diplopia and pain in the calves. The 6 patients whose course was progressive first complained of numbness and weakness of extremities, disturbance in gait or mental changes. It is possible that the presenting complaints in the patients whose course was intermittent were due to small plaques, while the symptoms of those with a progressive course were the result of larger plaques. Some observers (Putnam [8] and others) have stated the belief that symptoms due to small lesions tend to regress, while those due to larger lesions are apt to be permanent.

Mental symptoms involving the intellectual and emotional sphere were present in 6 of our patients. Of this group, intellectual deterioration played a prominent part in the clinical picture of 4 patients.

The diagnosis of multiple sclerosis is unusually difficult when the onset of symptoms occurs after the age of 40 and may be confused with such conditions as neoplasm of the spinal cord, generalized cerebral arteriosclerosis, cerebrospinal syphilis, cerebellar disease, amyotrophic lateral sclerosis, progressive spinal atrophy, syringomyelia, combined system disease and presenile psychosis. In only 2 of our 9 verified cases was the diagnosis of multiple sclerosis made during life, and in both the symptoms developed early in the fifth decade of life and the course was intermittent. In 3 cases an exploratory laminectomy was made because of the predominance of signs referable to the spinal cord with a progressive course. In 1 case the diagnosis was vascular myelopathy; in another, unknown degenerative disease of the nervous system; in a third, olivopontocerebellar atrophy, because of the severe ataxia, and in still another, cerebral arteriosclerosis.

Several factors are important in establishing the diagnosis of multiple sclerosis in the latter years of life: (1) the awareness that multiple sclerosis often begins during or after the fifth decade; (2) more frequent progressive course of the disease; (3) more frequent evidence of loss of intellectual capacities; (4) greater evidence of disease of the anterior horn cells, and (5) a tendency for the signs and symptoms to be more localized, i. e., less clinical evidence of multiple lesions.

## SUMMARY

In a series of 310 patients with multiple sclerosis admitted to the Montefiore Hospital, the onset of symptoms after the age of 40 occurred in 41 (13 per cent). Of 42 patients with multiple sclerosis on whom autopsy studies were made at this hospital, 9 (21 per cent) had onset of the disease during or after the fifth decade of life.

The diagnostic criteria of multiple sclerosis in the latter years of life differ from those of the younger age group in the following respects: a tendency to a progressive course, more marked evidence of intellectual deterioration and less evidence of dissemination of lesions. The most important single factor in the diagnosis of multiple sclerosis in the latter years of life is the awareness that the onset of symptoms is not infrequent after the age of 40.

Montefiore Hospital.

6. The exclusive incidence of Jewish patients in this series is due to the fact that the patients admitted to the Montefiore Hospital are predominantly Jewish.

7. Birley, J. L., and Dudgeon, L. S.: Clinical and Experimental Contribution to Pathogenesis of Disseminated Sclerosis, Brain **44**:150, 1921.

8. Putnam, T. J.: Multiple Sclerosis and "Encephalomyelitis," Bull. New York Acad. Med. **19**:301, 1943.

# EPENDYMITIS AND MENINGITIS DUE TO CANDIDA (MONILIA) ALBICANS

## REPORT OF A FATAL CASE OF MENINGITIS, WITH COMMENT ON ITS CLINICAL, BACTERIOLOGIC AND PATHOLOGIC ASPECTS

ARTHUR A. MORRIS, M.D.; G. G. KALZ, M.D., AND E. S. LOTSPEICH, M.D.
MONTREAL, CANADA

Meningeal involvement due to Candida (Monilia) albicans has been described so rarely that the report of a fatal case of meningitis caused by this organism seems justifiable. In the available literature only 2 previously reported cases with definitely established diagnosis were found, 1 by Smith and Sano [1] and 1 by Miale.[2] It is questionable whether infections of the central nervous system with Candida albicans are actually as rare as the literature seems to indicate or whether the condition remains undiagnosed in a considerable number of cases because of the difficulties which the classification of the fungi imperfecti present for the bacteriologic laboratory. The latter point seems to be substantiated by the survey of Freeman,[3] in which, besides the well established infections with Torula histolytica, Blastomyces and Coccidioides, cases of meningitis due to "Endomyces" and "Saccharomyces" with questionable or no bacteriologic studies are cited. The excellent article by Martin, Jones and associates [4] on the classification of Candida should prove of great value to the bacteriologist without any special training in mycology.

### REPORT OF CASE

L. S., a 23 year old white Frenchman, complained of dull, intermittent frontal headaches for ten months prior to admission to the hospital. Three months prior to admission he began to notice gradual diminution of vision and diplopia. Two months prior to admission he had a tooth extracted. Shortly afterward he suffered from pain over the vertex, after which his headache became so severe that he was forced to seek hospitalization. Two weeks prior to his admission examination revealed marked vertigo, insomnia, shortness of breath when lying down, constipation for three days, indigestion, progressive amblyopia, scotomas, tremor of the tongue and bilateral papilledema. Three days prior to his admission partial right hemiparesis was noted. Roentgenographic examination of the skull revealed no abnormality; the Wassermann reaction of the blood was negative; the blood sugar measured 88 mg. per hundred cubic centimeters; lumbar puncture revealed a pressure of 550 mm., with 284 lymphocytes per cubic millimeter of fluid. The sugar content of the cerebrospinal fluid was 23 mg. and the protein content 66 mg. per hundred cubic centimeters. Because of the pronounced increase in the cerebrospinal fluid pressure, the patient was transferred to the Montreal Neurological Institute, with the diagnosis neoplasm of the third ventricle.

General physical examination revealed that the patient was well developed but poorly nourished and somewhat emaciated. He complained of severe bifrontal and bitemporal headaches, which were greatly accentuated by any movement of the head or body. There was marked tenderness in the right temporal region to percussion and palpation. There were a moderately diminished light reflex in the right tympanic membrane, a reddened tongue, a slightly reddened and edematous pharynx and loss of a number of the upper and lower teeth. The tongue showed a white exudate from its anterior tip back into, and including, the posterior portion of the pharynx, particularly on the left side. The gums were markedly hypertrophic, especially around the incisor teeth. Mycotic-like lesions were distributed over the chest and trunk, and there was evidence of mycotic infection in the mouth and of mycotic dystrophy of the nails of the ring and index finger of the left hand and the nails of the thumb and little finger of the right hand. Epidermophytosis was present between the toes. The temperature was 100 F., the blood pressure 112 systolic and 70 diastolic, the respiratory rate 20 and the pulse rate 70 per minute. The mental status was difficult to evaluate, owing to poor cooperation and severe temporal and frontal headaches. Bilateral papilledema with hemorrhages and exudates, particularly conspicuous in the right retina, was noted. There was bilateral palsy of the sixth nerve, which was more pronounced on the left side. The patient complained of diplopia on looking to the left, and there was ptosis of the left lid. He lay in bed holding his head to the left side and slightly forward, as this position gave him the least amount of headache. Any change in the position of the head

From the Department of Neurology and Neurosurgery, McGill University and the Montreal Neurological Institute, and the Department of Bacteriology, McGill University.

1. Smith, L. W., and Sano, M. E.: Moniliasis with Meningeal Involvement, J. Infect. Dis. **53**:187-196, (Sept.-Oct.) 1933.

2. Miale, J. B.: Candida Albicans Infection Confused with Tuberculosis, Arch. Path. **35**:427-437 (March) 1943.

3. Freeman, W.: Fungus Infections of the Central Nervous System, Ann. Int. Med. **6**:595-607 (Nov.) 1932.

4. Martin, D. S.; Jones, C. P.; Yao, K. F., and Lee, L. E., Jr.: Practical Classification of Monilias, J. Bact. **34**:99-129 (July) 1937.

produced severe increase in headache. There were moderate hypertonia, particularly on the right side, and moderate stiffness of the neck. The Kernig and Brudzinski signs were present, and the knee jerks were greatly diminished.

On the night of his admission the temperature returned to normal and his headache subsided. On the second day in the hospital a roentgenogram of the chest showed the left border of the heart shadow to be slightly indistinct, with prominent bronchial-vesicular markings at the bases of both lungs and some accentuation of the root shadows, particularly on the right side. A ventriculogram performed on the second day in the hospital revealed considerable enlargement of both lateral ventricles; the septum pellucidum and the third ventricle were in the midline. There was pronounced enlargement of the third ventricle, and the aqueduct of Sylvius ran slightly farther posterior than might be expected; but the fourth ventricle was visualized, and it did not appear to be displaced. Some of the oxygen had escaped and outlined the interpeduncular cistern. The suggestive block in the neighborhood of the anterior part of the interpeduncular system was typical of meningitis. After the ventriculographic examination the patient's temperature rose to 104 F., and he was placed under treatment with intravenous injections of sulfadiazine. By the following day his temperature had returned to normal, only to rise to 100.5 F. in the late afternoon. Oral administration of sulfadiazine, 1 Gm. every six hours, was maintained for the following thirty-one days. During this time the temperature remained normal. The patient began to moan night and day because of pain behind his eyes and severe headaches. Two courses of potassium iodide therapy failed to give improvement. His headaches then became associated with moderate nausea and occasional bouts of vomiting, and it was suggested that, because of his delirium and increasingly severe headaches, which were not relieved by lumbar puncture, some other type of therapy should be instituted. High voltage roentgen therapy was begun to the base of the skull and administration of the sulfonamide drug discontinued on the thirty-third day in the hospital. He was then maintained on daily high voltage roentgen therapy for the following fourteen days, receiving a total of 2,700 r to the base of the brain and the cervical portion of the cord. No demonstrable improvement could be attributed to the roentgen therapy. He continued to be nauseated, had occasional attacks of nausea and vomiting and took fluids poorly; supplementary intravenous injections were frequently necessary. He continued to complain of headaches in spite of frequent administration of acetylsalicylic acid and acetophenetidin and occasional use of analgesics. After the completion of roentgen therapy, he became restless, complained of severe headache and showed increasing delirium, but the cerebrospinal fluid pressure had returned to below 200 mm. of fluid. Beginning on the fiftieth day in the hospital, he complained of severe toothache and extreme abdominal distention, which was relieved by daily catheterization. At this time he failed to respond to painful stimulation. Four days later, his temperature rose to 106 F., and he died of respiratory failure.

Studies of the cerebrospinal fluid on his admission revealed 29 mg. of proteins, 72 mg. of sugar and 727 mg. of chlorides per hundred cubic centimeters. There were 287 mononuclear cells per cubic millimeter of cerebrospinal fluid, and many round, double refractile bodies were seen on microscopic examination. The ventricular fluid showed the same double refractile bodies, consistent with the presence of fungus pathogens. Examinations of ventricular fluid for tubercle bacilli gave negative results. Specimens of cerebrospinal fluid and of ventricular fluid were sent to the department of bacteriology for cultural studies and identification. The urine on his admission was normal. Daily lumbar puncture showed a steady increase of protein in the cerebrospinal fluid, ranging from 29 to 222 mg. per hundred cubic centimeters. The sulfadiazine level of the blood during the period of chemotherapy ranged from 6.5 to 13 mg. per hundred cubic centimeters. Daily lumbar puncture during the patient's entire stay in the hospital revealed a pressure between 210 and 750 mm. + of fluid. After the diagnosis of basilar meningitis, daily lumbar puncture, with complete spinal drainage, was carried out, with relief of the severe headaches. The fluid was always bright yellow. The patient complained bitterly of toothache in the right lower jaw. Pus was seen draining from the pocket of the tooth, and cultures of this pus yielded Candida (Monilia) albicans.

## BACTERIOLOGIC STUDIES

The yeastlike fungus, which was later identified as Candida albicans, was isolated from eight specimens of cerebrospinal fluid intra vitam, from the thrushlike lesions in the patient's mouth, from pus of a draining dental abscess and from the specimens taken at autopsy (exudate at the base of the brain and the abscess of the scalp over the burr hole). The specimen obtained from punctures of the lung (bronchopneumonia of the lower lobe of the left lung) yielded only the usual organisms of the respiratory tract, with large numbers of Hemophilus influenzae. The blood cultures were sterile, and no fungi could be isolated from the scrapings of the patient's nails.

The first specimen of cerebrospinal fluid, received on April 4, consisted of approximately 4 cc. of almost clear fluid with a slight yellowish tinge. No pellicle formation was noted. After centrifugation a small amount of a slightly flaky sediment was obtained, adherent to the wall of the tube. No tubercle bacilli were found in stains for acid-fast organisms. Gram's stain of the sediment showed mainly mononuclear cells and some red blood corpuscles. After a prolonged search, a few gram-positive oval and round budding cells were seen. A hanging drop preparation showed a few round and oval budding cells with a vacuole and one or two highly refractile bodies. Only one elongated form, which was thought to be a mycelium, was found.

To exclude any possible contamination, a second specimen was requested, and examination showed the same type of organisms. A preliminary diagnosis of meningitis, due to a yeastlike fungus, was made. The cerebrospinal fluid was planted on blood agar plates, Brewer's meat mash and Sabouraud's agar slants. One set was incubated at 37 C. and one set kept at room temperature. After twenty-four hours the slants at 37 C. showed small, smooth, glistening colonies, creamy white in color. No visible growth appeared at room temperature until forty-eight hours after planting. After forty-eight hours the growth characteristics at 37 C. and those at room temperature were similar. The colonies increased in size but remained smooth. Hanging drop preparations from these young cultures on Sabouraud's solid medium revealed only round and oval budding cells (approximately 5 to 6 microns in

diameter) containing a large vacuole and some refractile bodies. The colonies on the blood agar plate after twenty-four hours were small and grayish white and showed the same morphologic characteristics as the colonies on Sabouraud's slants. In Brewer's medium a slight turbidity was noticed after twenty-four hours, which developed into a flaky layer in the intermediate zone, and a wet preparation from a five days' growth revealed the same type of budding cells but some rudimentary mycelial elements as well. Mycelial development on Sabouraud's slants was first noted after three weeks' incubation as fine threads growing into the medium and forming tufts. The cultural characteristics have changed remarkably little in the three months of observation prior to this report. After about four weeks' incubation on Sabouraud's agar slants, differentiation of the colonies into two types could be readily distinguished—one type remained low convex and smooth with a well defined circular outline; the other type developed a honeycomb center, some radial grooves in the border and a slightly lobed margin. These two types of colonies were obtained from the same specimen at room temperature and at 37 C. In our opinion, the differentiation was due entirely to the amount of moisture on the slants, as the former type of colony was found regularly on the slants inoculated with a fair amount of spinal fluid and the latter when sediment only was used as inoculum. It seems important to note this observation, as some authors have attached diagnostic value to the gross appearance of colonies.

After a short observation on the cultural and morphologic characteristics, we followed the valuable method suggested by Martin, Jones and associates[4] for the final identification of the organism. The necessary mediums were prepared by following exactly the formulas given by the aforementioned authors. The morphologic, cultural and biochemical characters of the strains isolated during the lifetime of the patient and those obtained post mortem were identical. Sabouraud's dextrose acid broth, after forty-eight hours' incubation, showed a heavy sediment but no surface growth. The colonies on blood agar plates, aften ten days' incubation, were approximately 1 to 2 mm. in diameter and circular with entire edge and possessed a slightly convex, smooth surface and grayish white color. The carrot plugs have been under observation for more than three months. No asci could be found at any time on repeated examinations. The fermentation reactions were uniform in the special carbohydrate broth (inoculated after three transfers from sugar-free medium and incubated in sealed tubes for ten days).

| Dextrose | Saccharose | Lactose | Levulose | Maltose |
|---|---|---|---|---|
| Acid; gas | Acid | — | Acid; gas | Acid |

A stab culture in a corn meal agar tube produced the "inverted pine tree" type of growth in three to four days.

The slide culture technic on corn meal agar proved rather difficult in obtaining uniform results. Only one out of five or six slide cultures showed a well developed "treelike" mycelium, with the ball-like clusters of spores along the hyphal threads and the terminal chlamydospores. The best results were obtained by inoculating the slide before the medium was completely solid.

## PATHOGENICITY TESTS

*Rabbits.*—One rabbit was inoculated intravenously with 1 cc. of a 1 per cent suspension from a twenty-four hour growth on Sabouraud's medium (Benham[5]). The rabbit died forty-eight hours after inoculation. A summary of the postmortem examination follows. No gross lesions could be found in the lungs, liver or spleen. Careful examination of the heart muscle revealed a few very small abscesses. The kidneys showed extensive abscess formation, mainly in the cortex. These lesions were described as typical of infections with C. albicans in rabbits by Benham[5] and by several other authors. The brain showed a slightly purulent exudate over the entire surface, more prominent at the base. No lesions could be demonstrated in the brain itself. Smith and Sano[1] found abscesses in the brain of the rabbit inoculated with a strain of C. albicans isolated from an infant with fatal meningitis and

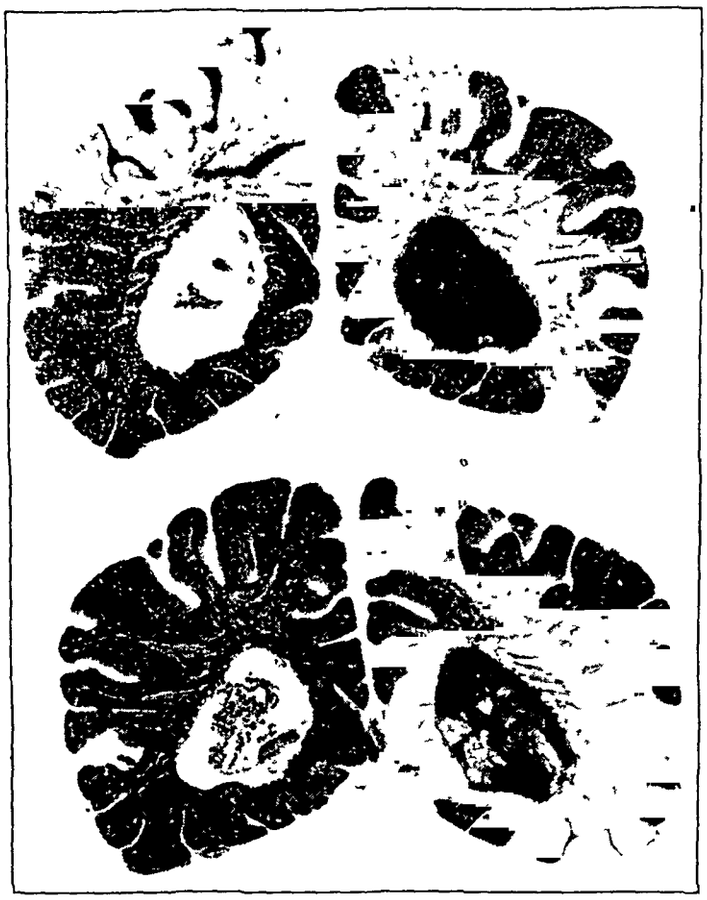


Fig. 1.—Coronal sections of the brain, showing symmetric enlargement of the ventricles. Large amounts of granular, white exudate cover the ependymal surfaces, particularly the choroid plexus, and bridge the ventricles.

septicemia. We isolated C. albicans from the heart blood, the heart muscle, scrapings from the lungs, liver, spleen and kidneys and the exudate of the brain. Direct smears, stained and unstained, of the pus from the abscesses and exudate showed the budding cells and large numbers of mycelial threads. Intracutaneous injections into a rabbit of 0.2 cc. of a 1 per cent suspension caused formation of an abscess in forty-eight hours, from which C. albicans was isolated.

*Guinea Pigs.*—Intraperitoneal injections of 1 cc. of a 1 per cent suspension had no ill effects. The guinea pig is still alive and well, four months after injection.

*White Mice.*—Intraperitoneal injections of 2 cc. of a 1 per cent suspension had no ill effects. One mouse

5. Benham, R. W.: Certain Monilias Parasitic on Man: Their Identification by Morphology and by Agglutination, J. Infect. Dis. **49**:183-215 (Sept.) 1931.

was killed two weeks after injection, but no lesions were seen and cultures of material taken from various organs remained sterile. The second mouse was killed ten weeks after inoculation. No lesions were found, and cultures yielded no growth. Four more white mice were given intraperitoneal injections of various amounts of a heavy suspension from a twenty-four hour growth on Sabouraud's medium. One mouse given an injection of 5 cc. intraperitoneally died twenty-four hours later and showed a very pronounced nodular peritonitis, from which C. albicans was grown in pure cultures. No growth was obtained from any of the other organs. The 3 other mice died after sixteen to eighteen days. No lesions were found either on macroscopic examination or on histologic study of sections from various organs. No growth was obtained on culture.

Serologic studies were not attempted, since immune serums against the various members of the genus Candida are not at our disposal. From the therapeutic standpoint, it was of interest that this strain of C. albicans was not susceptible to penicillin (i. e, in vitro).

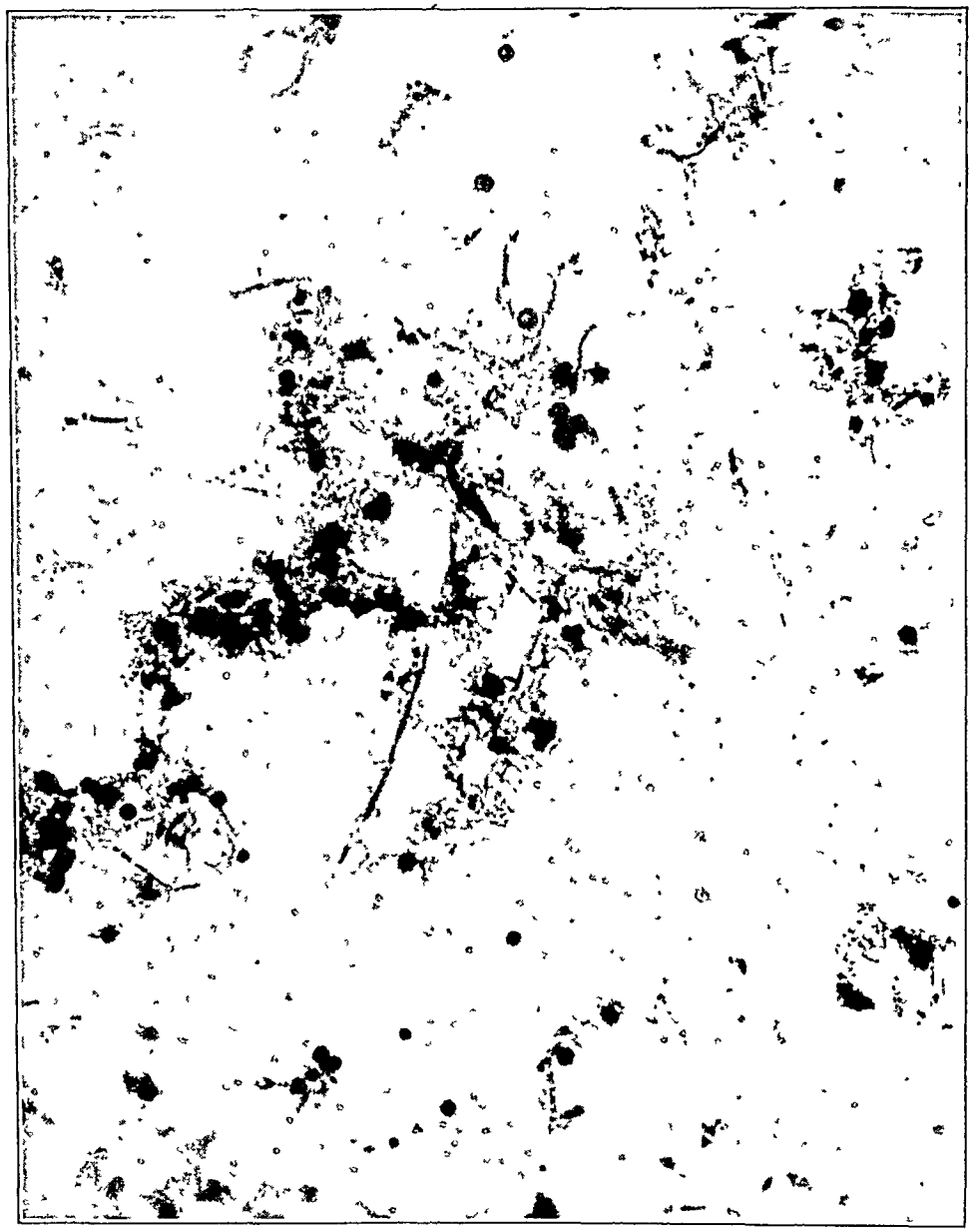


Fig. 2.—Smear taken from the ependymal exudate, showing numerous mycelial threads, as well as many round, gram-positive bodies, somewhat larger than lymphocytes.

## PATHOLOGIC OBSERVATIONS

At autopsy the epidural and subdural spaces appeared normal. The brain weighed 1,430 Gm. The subarachnoid space was filled with a grayish white exudate, which extended to involve the base and the upper cervical portion of the spine. Coronal section showed that the ventricles were symmetrically dilated and contained large amounts of granular, grayish white exudate, covering the ependymal surfaces, particularly the choroid plexus, and bridging the ventricle at several places. The exudative reaction was considerably greater within the ventricles than within the subarachnoid space.

Microscopically, the ependymal lining had largely disappeared, and an exudate consisting of lymphocytes, necrotic debris and numerous mycelial threads lined the ventricular cavities. Large numbers of multinucleated giant cells were present. Fibrous repair had

aken place in some areas. In the adjacent portion of the brain, perivascular infiltration with round cells and phagocytes was seen. There was increase in the glial nuclei. Over certain areas where the ependyma had been replaced the exudate had organized to form a granuloma consisting of large numbers of multinucleated giant cells. Myceliums were seen in large numbers throughout the exudate.

A section through the thoracic portion of the cord showed a minimal amount of exudate, consisting of lymphocytes and some fibrous thickening of the meninges.

*Comment.*—Unlike the case reported by Smith and Sano,[1] the reactive process quantitatively was greater in the ventricular walls than in the subarachnoid space. Since fibrin, scarring and small granulomas were observed in the ependymal reaction, the process must be considered as subacute or chronic.

## GENERAL COMMENT

This case illustrates many interesting features of clinical, pathologic and bacteriologic interest. Clinically, the diagnosis made prior to the patient's admission to the Montreal Neurological Institute was "tumor" of the third ventricle, probably ependymoma. Actually this was an accurate diagnosis, for the pathologic lesions showed "a tumor of fungus" in the areas where the choroid plexus was most extensive. On the patient's admission to the hospital, in view of the positive Kernig and Brudzinski signs and the moderate stiffness of the neck, associated with a cell count of 284 monocytes per cubic millimeter of cerebrospinal fluid, a diagnosis of tuberculous meningitis was made, but because of the severity of the headaches, the danger of lumbar puncture with bilateral papilledema and a few signs of an expanding lesion in the posterior fossa, largely on the right side, a ventriculographic examination was made to determine the presence of the pathologic process. This revealed a block in the upper portion of the interpeduncular cistern, consistent with a diagnosis of meningitis. The organisms were seen on routine examination of the cerebrospinal fluid and were suspected to be either Blastomyces or T. histolytica. Routine and special bacteriologic cultures then revealed the fungus to be C. albicans, so that an accurate clinical diagnosis was in our hands long before the death of the patient. Treatment was apparently of no avail. First an adequate course of sulfadiazine, with a blood level of between 6.5 and 13 mg. per hundred cubic centimeters, was maintained for the first thirty-three days in the hospital, during which time the temperature remained perfectly normal. However, the patient still had symptoms of headaches, nausea and vomiting, and increasing delirium, increasingly severe toothache and stiffness of the neck, with occasional abdominal distention, diplopia, retro-orbital pain and gradually increasing disorientation, so that some other form of therapy was considered necessary. Then, sulfonamide therapy combined with administration of potassium iodide by mouth was tried over a period from the twentieth to the thirty-fourth day in the hospital, during which time the patient failed to improve. Finally, high voltage roentgen therapy for a period of fourteen consecutive treatments, from the thirty-fourth to the forty-eighth day in the hospital, was apparently without avail. While under roentgen therapy, and immediately after completion of the first treatment, his temperature rose to 102 F. and remained elevated until his death. As far as could be determined clinically, roentgen therapy offered no relief of symptoms in this case.

It was stated by Miale[2] that mononuclear cells in the cerebrospinal fluid described in his case may have been mycotic pathogens. In the present case, the double refractile, yeastlike organisms were recognized in routine examination of the cerebrospinal fluid and gave a clue as to the cause of the meningitis.

Laboratory studies were not helpful in making the diagnosis prior to the patient's admission, for in a single determination the sugar content of the cerebrospinal fluid was reported as 23 mg. and the protein as 56 mg. per hundred cubic centimeters. The chloride content was not reported prior to his admission. However, on admission the protein of the cerebrospinal fluid measured 29 mg., the sugar 72 mg. and the chlorides 727 mg., per hundred cubic centimeters. In view of the moderate reduction of sugar and the presence of a normal chloride content of the cerebrospinal fluid, tuberculous meningitis seems unlikely. Therefore, in this respect the cerebrospinal fluid did help in making a clinical diagnosis other than that of tuberculous meningitis. The spinal fluid sugar in the case reported by Miale[2] was always too low to be read, but this was not so in our case, as the sugar in the cerebrospinal fluid ranged from 23 mg. on the patient's admission to 72 mg., per hundred cubic centimeters, on the second day in the hospital.

It is interesting to note that, as in the case reported by Miale,[2] Candida organisms were isolated from the pus of a previously extracted tooth and similar organisms were demonstrated in material obtained from lesions in the pharynx, from exudate over the tongue and from the gums. Whether generalized invasion of the blood stream by mycotic pathogens or direct extension

by way of the cribriform plate was responsible for the meningitis is not known. The fact that Smith and Sano [1] were able to produce focal damage to the brain, as well as meningitis, by the intravenous injection of Monilia pathogens into rabbits, previously obtained from a human patient, would seem to support the belief that invasion of the blood stream takes place and that perhaps a special neuropathic strain of Candida (Monilia) exists. This patient presented rather a mycotic museum, there being obtained evidence of infection with three fungi: (1) Epidermophyton, from the feet; (2) Taenia versicolor, from the back, and possibly of the finger nails, and (3) C. albicans, from the meninges, cerebrospinal fluid, ventricles and brain.

This case is also unique in that the primary diagnosis of cerebral tumor was made in the early stage of the disease. Later, tuberculous meningitis was considered as the most likely possibility. Only until a ventriculogram was made was the diagnosis of meningitis conclusive. Relief of symptoms was at first gained only by repeated lumbar punctures, in an attempt to maintain a normal cerebrospinal fluid pressure. The rapidly accumulating hydrocephalus was due to a block in the interpeduncular system, interrupting the normal circulation over the surface of the brain by way of the subarachnoid space to the longitudinal sinus.

3801 University Street.

# NARCOLEPSY

## I. COMBAT EXPERIENCE OF A SOLDIER WITH NARCOLEPSY

MAJOR HOWARD D. FABING

MEDICAL CORPS, ARMY OF THE UNITED STATES

An unusual opportunity presented itself for the study of narcolepsy in a combat soldier. This patient began to have symptoms in 1935, and his disorder was not recognized correctly in premilitary life or in the precombat period of his military career. As a result he went through two long campaigns in the Mediterranean Theater of Operations. The unusual nature of his experiences not only provides an interesting story but throws some light on the pathogenesis of this disorder.

### REPORT OF A CASE

*Family History.*—The patient's father, a Scotch-Irishman, died at the age of 64, of cerebral hemorrhage. His mother, aged 69, is living and well. The patient is the sixth of 8 siblings. A brother and a sister died of traumatic causes; the remainder are living and well except for a sister aged 38, the fifth sibling. She is described as being "highstrung"; she ran away from home at the age of 15, has been married three times, remains under a doctor's care at all times, is ill tempered and constantly involves her family and neighbors in useless altercations. From the patient's description, this sister appears to have an aggressive, as well as an inadequate, psychopathic personality. No other neuropsychiatric illness in the family is known to the patient.

*Premorbid History.*—The patient was born in 1909 in Missouri. After he left school, at the age of 13, where he had completed the sixth grade without failures, he worked on a farm with his father. When he was 16 years old, the family moved to Independence, Mo., where he worked successively as delivery boy, grocery clerk, laborer, foundry worker and truck driver. At the age of 20 he got a job as a gardener and married that year. For the next twelve years, with the exception of one year spent in driving a team of mules on a highway construction job, he continued as a gardener in the summer and a trapper in the winter. During the autumn he traveled through Iowa and Missouri as a corn shucker. He became a sod contractor and employed three men. He learned the stone mason's craft as well. He enjoyed outdoor activities and sports, was a hard worker and had excellent health. His past medical history disclosed that he was never seriously ill before the onset of his present trouble. His only contagious diseases were pertussis, measles and mumps. He gave no history of influenza.

*Present Illness.*—In 1935 he began to fall asleep at his work while driving a team of mules. He drowsed with the reins in his hands and wakened when his fellow workers on the road job shouted at him. The short attacks of diurnal sleep have continued since that time. About five months after the onset of the disorder he was hunting with his brother. A rabbit came into view and he raised his gun to shoot; but suddenly his arms and neck began to quiver, and, in his own words, "everything gave way under me and I squatted like a wet rag." Though fully conscious, he remained powerless on the ground for approximately a minute.

After that episode attacks of tonelessness, as well as sleep attacks, were severe. He had to abandon hunting because as a rabbit jumped up he would lose muscular tone and fall to the ground. The noise of the rise of a covey of qail would startle him so that he could not get his gun up into firing position, and when he regained his use of his muscles the quail were well away. He had to abandon the hunting of squirrels because he invariably fell asleep under trees while looking for them. On the other hand, he continued raccoon hunting, watching his dog kill the animals, enjoying the fight but never experiencing a cataplectic attack during these episodes.

He enjoyed boxing but had to give it up because of repeated cataplectic seizures. He stated that he never lost tone as a result of a stinging blow but that "when I got to mixing it up and laughing I'd always go down in a heap." He had to abandon playing baseball as well because he had a cataplectic attack one day in the simple act of trying to catch a pop fly. As is the case with many narcoleptic persons, he avoided raucous laughter as much as he could. He tried not to "feel tickled" at funny stories, avoided pranks and practical jokes on his friends and developed the technic of responding with hollow laughter to humorous situations.

On two occasions he almost drowned during cataplectic attacks. One evening he dived into a small lake, and as he came to the surface he felt an attack coming on. He made one frantic stroke toward the shore but went limp and sank. His brother rescued him, and his muscular tone returned quickly. On a second occasion he was wading in a shallow creek, "hogging" fish. He grasped a large one, which struggled violently as it broke the surface. This exciting display caused a cataplectic attack. He went limp, sank in the water and lost the fish. The timely assistance of a friend kept him from drowning. After these episodes he gave up water sports.

Careful inquiry revealed that pain, anger, shame, grief or worry never caused cataplexy in this patient. Numerous painful accidents while he was working with tools, a painful fracture of a metacarpal bone and a painful head injury did not cause an attack. Angry arguments were never followed by cataplexy. He told of an angry fist-fight which landed both the patient and his adversary in jail, but which was unassociated with any attack. The shame he experienced over this episode and his subsequent trial did not precipitate a seizure. Grief, such as he experienced

at his father's death, and worry over domestic difficulties failed to produce the attacks.

He began to have cataplectic attacks during sexual intercourse within a year of the onset of the disorder. He stated that during the act, just before an orgasm occurred, he would suddenly have a cataplectic attack and go completely limp. These spells would last approximately one minute, during which time penile erection was invariably lost and ejaculation failed to occur. As a result he had to abandon this activity, in which he had formerly taken keen pleasure, and his wife began to run around with other men. He wore the cuckold's horns for more than a year with good grace, but when his wife became pregnant by another man he left her and went to Los Angeles, where he worked in a defense plant until his induction into the Army.

*Military History.*—He was inducted into the military service on May 3, 1942, at Fort Leavenworth, Kan., and received his basic training at Fort Sill, Okla. He stated that he often fell asleep during "breaks" in the training schedule. His basic training was with the 105 mm. howitzer gun. In July 1942 he was sent to Indiantown Gap, Pa., and was assigned to a field artillery battalion with the rank of private first class. He sailed for Scotland in August 1942. Aboard ship, he was interested in observing gunnery practice, and this occasioned no cataplectic attacks. In Scotland he met a woman and attempted to have sexual relations with her, but a recurrence of his cataplectic attacks during intercourse caused him to abandon this relationship. During the remainder of his precombat training, he had no trouble except for recurrent sleep attacks during training problems. He embarked for the African invasion in October 1942, and on the second day at sea an explanation of the landing operation was given by his commanding officer. The unit was keyed up and eager for combat. There were sharpening of knives and careful inspection of equipment. He looked forward to combat keenly.

*African Invasion.*—His unit struck the African coast at Blue Beach, near St. Cloud, east of Oran, at about 8 a. m. on November 8. No opposition was met at the landing, and the patient had no symptoms. He saw two dead Arabs, one dead soldier and one wounded soldier. This provoked no attacks. His unit formed itself and marched 5 miles (8 kilometers) inland, then went into an orchard until midnight of the first day, waiting for their guns to come up. The constant rattle of rifle fire from infantry units committed in combat before St. Cloud could be heard ahead of them. The patient stated that as soon as he had dug a foxhole he fell asleep in the hole and slept through the night. In the morning he carried ammunition, and when his job was done, he slipped off and spent most of the day in the foxhole asleep. On the third day the battery moved into a wheat field, where it immediately went into gun position and fired approximately one hundred rounds. His job in the gun crew was that of no. 7, preparing charges of ammunition. He experienced no trouble during his first combat firing mission, even though a shell hit about 75 yards (68.5 meters) behind his battery. After the French capitulation his battery proceeded through the town of St. Cloud, where he saw the scattered corpses of twenty to twenty-five mules and enemy soldiers heaped along the side of the road. He did not respond to these grim sights with cataplexy. He felt after the first days of combat that he could "take it O. K."

His unit moved immediately up into Tunisia, in support of British troops in their attempt to seize the country. The battery was set up in a cemetery below Long Stop Hill. The Germans were in position on the hill, and the tactical mission of his group was to take the hill. They became engaged on Christmas Eve. On Christmas Day his unit was shelled badly. Two members of his battery were killed. He saw them immediately after they were hit. No cataplectic attack developed. The Germans pounded his area severely with 88 mm. shells. The battery commander ordered the men into foxholes. He remained in his foxhole almost the entire day, pinned down by enemy fire. The one road out from their position was under constant shelling. He became extremely jittery and "got the shakes." He became more frightened when infantry units retreated through the area and the realization came that his battery was literally in the front line. Despite this, while in his foxhole, he slept on and off throughout the day. One shell struck about 50 yards (45 meters) away and wakened him. He could hear the cries of his comrades for the "medics," and he knew that some one had been hit. He fell back asleep soon thereafter. Later he was wakened by another soldier, who jumped into his foxhole. After waking he was "plenty scared" and thought his unit would be wiped out entirely. He stated, "I am not much of a hand for prayer, but I thought surely that my end was near that day." On Christmas night the battery disengaged itself and moved back to Medjez-el-Bab, where it remained dug in for the next six weeks.

During January 1943 he was on a roving gun assignment, which lasted approximately one week. One night during this period his outfit got word that German patrols had penetrated the American infantry. The entire battery was posted for guard duty. Guards were placed approximately 100 feet (30 meters) apart. He was crouched in a foxhole, and at about 9 p. m. he saw a moving shadow. He challenged the man, but the wind was blowing the wrong way and the man did not hear the challenge. The patient followed the shadow and saw the man step behind the shadow of a tree. He jumped out of his foxhole, put a shell into his rifle and threw the bolt. He was about to squeeze his trigger when the other man said, "Don't shoot, Sleepy; it's Jim." At that the patient went into a heap, and his gun fell from his hands. The other man rushed forward to see what was the matter. By the time he had crossed the hundred feet of space between them, the patient had regained his motor power. This cataplectic attack, which occurred when he was about to shoot his friend unwittingly, proved a most upsetting experience, and he remained jittery all night after the episode.

After leaving the Medjez-el-Bab area his battery swung south to the region of the Kasserine Pass. In a flank maneuver, the Germans gained a position of vantage, and the ensuing week was punctuated by great activity; his battery fired approximately four hundred rounds during that time. He states that if he sat down he fell asleep, whether at the gun or at the ammunition pit, 12 feet (3.6 meters) away. During that week of severe combat he often fell asleep between the trails of the gun. It was at this time that he earned the universal nickname of "Sleepy." His fellow G.I.'s often remarked, "I wish I could sleep like you do," or "I don't see how in the hell you can sit down and go to sleep with shells busting all around you."

After the prolonged engagement in the Kasserine Pass area, his unit pressed forward to Gafsa and then on to El Guettar. The men spent the night digging

into position, and when morning came they found that the Germans were 300 yards (274 meters) distant. Just before daylight he was given the job of burying a fellow soldier, who had died. No cataplectic attack occurred as a result. When daylight came, it was reported that German tanks were maneuvering in the area. The patient became extremely apprehensive, could hardly stay still and kept moving around. His heart was pounding, and he had a quivering sensation throughout his entire body. While feeling that way, he volunteered to go forward to the mouth of the gully as a lookout. He was armed with a Tommy gun and crawled up forward approximately 100 yards (91 meters) to a place of vantage, where he stayed for an hour. A German tank 500 yards (450 meters) away was shelling a half-track 50 feet (15 meters) ahead of him. A duel between the half-track and the tank ensued. The tank was finally hit and knocked out. During this exciting display he experienced no cataplectic or narcoleptic attack. As he lay there he got over his shakiness; as he stated, "I figured to myself that if I had to get it, I might as well get it here as any place." After that he became calm. He watched the German tanks retreat, and then he went back to his post. He felt "wore out," and as soon as he reported he got into a foxhole and went to sleep.

He was awakened by the bombing of German planes coming directly overhead. A 200 pound (90.7 Kg.) bomb hit within 200 yards (183 meters). Communications between his battery and neighboring units were broken. The battery remained isolated all day and was subjected to dive-bombing throughout the day. During that time he had the jitters very badly. He asked his sergeant what he thought "they'd do to a fellow if he took off and got out of there," but he remained, at his sergeant's advice. Throughout the entire afternoon the patient was extremely jittery, vacillating between fleeing to the rear and remaining at his post. All the members of his unit were ordered to remain in their foxholes, but the patient could not stay in one hole. He said that another soldier, "a little Polish kid," and he "just kept moving from one place to another, from one foxhole to another, to the machine gun bed, to the kitchen, to the battery or back to a foxhole." He said that he was "shaking like a leaf" during the entire afternoon. No cataplectic spells or sleep attacks occurred. During that day his battery received eight attacks by infantry and by tanks.

As evening wore on, it became obvious that the position could not be held any longer. Orders were received to destroy the guns and to retreat. The order called for "every man for himself." In retreat it was necessary to scatter and to climb up over a hill. As the men of the unit scattered fanwise over the face of the hill, shell fire from the enemy rained all about them. The patient had to stop halfway up the hill to rest and catch his breath. While resting, an 88 mm. shell struck about 12 feet (3.6 meters) from him, and he saw shrapnel strike another man in the lower part of the back and wound him severely. The patient thought that surely his time was up. The face of the hill was covered with the fire from 88 mm. guns, machine guns and mortars, as 80 to 90 men were crossing 100 yards of exposed uphill terrain "while enemy stuff was dropping everywhere." While regaining his breath on the side of the hill, watching his entire unit in retreat, and while standing in the midst of the rain of enemy gunfire, he had no attack. He proceeded over the top of the hill and walked 3 miles (4.8 kilometers) back to a concentration area. He fell to the ground and slept immediately and continued to sleep the entire night.

After a period of relative quiet, the unit worked north to a position near Ferryville, where a German railroad gun began to lay down a sweeping fire. The patient was struck in the left shoulder by a piece of spent shrapnel. No cataplectic attack occurred. Later that afternoon an order came to fire five rounds at a particular target. After the first round the gun drew fire from the large railway gun which had shelled them during the morning. The whining of the oncoming shell could be heard long before it hit, and every one on the gun took off and ran to a slit trench 15 feet (4.5 meters) away. The patient had no cataplectic attack during this time. That was the last round of fire by his battery in Africa. Tunis fell later that day, and the campaign was over for his unit.

An estimate of the extent of his sleep attacks can be gained from the fact that one of his buddies appointed himself to the task of looking up the patient at every meal to make sure that he was not sleeping. He said, "I missed a lot of meals by being asleep. The fellows were good about it; and if they weren't too busy with other things, they'd come around and wake me up to get some chow."

After the Tunisian campaign he requested transfer from the gun section to the motor maintenance division, chiefly because in the new position he would not have to stand guard. He never permitted himself to lie down and sleep on guard duty, but he had the uncomfortable experience repeatedly of waking up while standing still or while walking his post. When "pulling" guard duty in pairs, he always insisted on walking the post and having the other man watch, in order to avoid sleeping. His sergeant knew of his affliction and relieved him of guard duty whenever possible, but, despite this consideration, he had averaged one to two hours a night at this duty throughout the campaign. The haunting dread that he might fall asleep on guard, jeopardize his unit and gain himself the death penalty prompted his request for transfer, which was granted.

*Sicilian Invasion.*—Before the Sicilian invasion the unit cruised along the African coast in an LCT for approximately two weeks. One afternoon the vessel put into a small harbor for water, and his buddies urged the patient to go swimming. On the first dive into the water, as soon as he came to the surface, he knew that a cataplectic attack was coming on. He struck out for a wooden ladder 6 feet (1.8 meters) away, took about two strokes and managed to hook his arm over a rung of the ladder. His head fell limp, and he began to slip into the water. His sergeant swam up to him, asked him what was the matter and helped him gain the ladder. Some seconds later he was able to say, "Nothing is the matter," and he climbed up the ladder and got out.

On the night before the invasion, during a heavy storm, his vessel became lost from its convoy. He was extremely frightened. Waves beat against the vessel and broke over its bow. He stated that he was probably "the scaredest one on the boat" and felt that he was surely going to drown. No cataplectic attacks occurred. After midnight the storm subsided, and he fell into deep sleep. He wakened near daylight, when his vessel was off the beach at Gela. There were five or six attempts to get close to the shore, but the vessel ran into shallows. Finally, a pontoon was rigged under the bows of the craft, and vehicles were run out onto the beach over the pontoon. During the laborious attempt to approach the beach, the patient was extremely tense and nervous. A landing craft near his own was hit by an aerial bomb, and the ammunition in its hold exploded violently. A German plane was shot down and landed in the water alongside his vessel. There

was great activity of small boats milling around, and as daylight came he could see the confused combat activity ahead of him on the beach. He was extremely frightened, and he stated that he had a helpless feeling during those anxious hours.

His unit proceeded inland immediately on landing and went into gun position in an almond orchard, about 3 miles from the beach. The Germans surrounded his battery with ten or twelve tanks, and some of them swung around and got between his gun position and the beach. The gun position got a bad raking by German tanks, and the patient had a severe shaking reaction. He could not remain where he was. In an aimless fashion, he wandered away from his battery and went into a vineyard to his left. He stated, "I was terribly scared, and I took off and sort of lost my memory then." He circled around through the vineyard toward the beach. Near the beach he found a haystack. He remained asleep until noon. During that time the air was filled with Naval shells sailing overhead at the enemy tanks. Finally, his battery disengaged itself and retreated to the vicinity of his haystack, where he was discovered and was wakened by his comrades.

The afternoon was quiet; but a paratroop landing in the area began after dark, and this provoked strong action on both sides. The night was filled with rifle and artillery fire. The patient, extremely frightened, could not remain in one place. In the company of his mess sergeant, he started for the beach. They proceeded ½ mile (0.8 kilometer) to the rear, but so many shell fragments from ack-ack guns were falling all about them that they felt it would be safer back at the battery, and they turned around. He fell asleep as soon as he returned to his battery position, although enemy action continued the remainder of the night. His unit recovered its position, then moved through the town of Gela, where there was much firing, and then to a village 8 or 10 miles (12 or 16 kilometers) inland.

Later on in the Sicilian campaign the battery got into position behind a mountain in the Randazzo area. The Germans were shelling a road in the vicinity with six-barreled mortars (*Nebelwerfers*). The missiles from these guns sound like airplanes in a power dive. When the guns opened up, the patient was sitting under a mulberry tree, playing poker. The game broke up quickly; and, in the company of 7 other soldiers, he jumped into a culvert under the road. Rocket mortar shells rained down on them, but he had no cataplectic attacks during the afternoon in the culvert.

During the remainder of the Sicilian campaign the patient, who was in the motor maintenance section, saw little of combat. After the termination of this campaign his unit went to Palma, in the south of Sicily, where they remained four or five weeks in bivouac. He came to England with his unit in November 1943 and remained with his battery for the next two months. One day he went on sick call to request acetylsalicylic acid for a persistent headache, which had begun in Sicily. While waiting his turn the patient fell asleep, and it was then that the medical officer came to the realization that his sleepiness was pathologic and sent him to the hospital. There a diagnosis of narcolepsy was made for the first time, and it was found that he responded favorably to administration of 15 mg. of benzedrine sulfate twice daily. The patient states that after he had been taking benzedrine it was the first time in nine years that he had been able to read a magazine or a book without falling asleep. While in the hospital there, he ran short of benzedrine sulfate tablets and was without them for one day. On the next day he played baseball, and during the game he had a cataplectic attack. As he was going into position to tag a runner at third base, he felt an attack of cataplexy coming on. He managed to stop the ball with his glove, but he went down in a heap and dropped the ball, and the runner piled on top of him.

*Diagnosis.*—The clinical diagnosis in this case can hardly be in doubt: The case is one of the narcolepsy-cataplexy syndrome. Physical examination revealed no evidence of a pathologic condition. Neurologic examination failed to disclose any evidence of disease of the central nervous system. The urine was normal; the hemogram was normal, and lumbar puncture released free-flowing, normal cerebrospinal fluid under 100 mm. of pressure. The basal metabolic rate was —4 per cent. Roentgenologic study of the skull revealed nothing abnormal. The absence of clinical, historical or laboratory evidence of preexisting disease of the brain places the case in the idiopathic, or cryptogenic, or undetermined, category. Some features of the case are unusual, but all have been noted before. Attacks of cataplexy at the moment of sexual orgasm were reported by Rothfeld.[1] The narcoleptic victim is sometimes "asleep on his feet" while walking or marching, as was this soldier while walking behind a team of mules or walking a guard post in Tunisia. Such trancelike states have been compared to the cataleptic attacks of the hysterical person. This patient gave no history of "nocturnal paralysis," as Wier Mitchell called it, or "sleep-paralysis" (Wilson), the condition in the crepuscular period between wakefulness and sleep in which the subject is fully conscious but is incapable of moving a muscle. The absence of anger as an excitant of cataplexy is not rare; hearty laughter is the only excitant in some cases. A shaking or nodding of the head at the onset of the attacks of cataplexy, which the patient reported, was first described by Westphal.

## COMMENT

The outstanding fact in this case is the paucity of cataplectic attacks during combat. Ample time was available over a series of evenings to review the patient's history minutely, and he was a good witness as well. Careful reflection and repeated review of his combat experience failed to reveal any other attacks than the two cited herein, i.e., the attack when inadvertently he almost shot his buddy and the attack while he was swimming off Bizerte. This is surprising in view of the magnitude of the affective experiences which were heaped on him. The repeated attacks of severe anxiety reactions of the "shakes" variety; a panic reaction on the occasion in Africa when he kept running from one foxhole to another despite orders to lie low, and an amnesic fugue, when he wandered off the battle field to a haystack near Gela, are all evidence of an acute, though abortive, combat neurosis and give testimony to the profound emotional reactions, with consequent disintegration of behavior, that occurred time and again in this soldier.

1. Rothfeld, J.: Ueber Orgasmolepsie und über sexuelle Erregungen bei narkoleptischen Schlafzuständen, nebst Bemerkungen zur Narkolepsiefrage, Ztschr. f. d. ges. Neurol. u. Psychiat. **138**:704-719, 1932.

I was surprised that so few cataplectic episodes had occurred, and I told the patient so. He countered with the statement that "being scared doesn't bring those falling spells on. I'm not ashamed to admit that I've been as scared as anybody ever was; and if being scared caused them, the boys would have been picking me up off the ground all the way from Oran to Troina." He went on to point out that it is not a state of fear, or a state of jollity or any emotional state which produces cataplexy, but, rather, that the condition is brought about by a massive stimulus. "It comes on when something big and sudden hits you, when you're not ready for it. Then you're down almost before you have time to have any feeling about it. Big, sudden things surprise my muscles almost before they surprise me. They've got to be big and fast, though, to knock me down," he insisted.

## SUMMARY

The case of a 35 year old soldier suffering from narcolepsy, cataplexy and trancelike cataleptic attacks is reviewed in detail. His disorder began seven years before his induction into the Army; and because it was not recognized he went through two major military campaigns. In combat he lived through many emotion-laden experiences, of a magnitude seldom endured by a patient with this disorder. Despite this, cataplexy was a surprisingly rare occurrence. The case, therefore, casts doubt on the accepted belief that cataplexy results from "emotional" stimuli.

# PSYCHOPHARMACOLOGIC STUDY OF SCHIZOPHRENIA AND DEPRESSIONS

## II. COMPARISON OF TOLERANCE TO SODIUM AMYTAL AND AMPHETAMINE SULFATE

JACQUES S. GOTTLIEB, M.D.; LIEUTENANT HOWARD KROUSE
IOWA CITY MEDICAL CORPS, ARMY OF THE UNITED STATES
AND
ARTHUR W. FREIDINGER, M.D.
IOWA CITY

Since the reaction of a psychotic patient to the intravenous injection of sodium amytal has been recognized as being of diagnostic,[1] therapeutic,[2] prognostic[3] and investigative[4] importance, attempts have been made to improve the response to this drug. Various stimulants of the central nervous system, such as caffeine and sodium benzoate,[5] metrazol[6] and amphetamine sulfate,[7] have been employed for this purpose: to improve the psychologic characteristics of the response, to decrease drowsiness and to prolong the reaction.

In a previous study,[8] the effects of combined intravenous injections of sodium amytal and amphetamine sulfate in patients with schizophrenia and depressions were compared. When a constant dose (sodium amytal, 250 mg.; amphetamine sulfate, 10 mg.) was used and the response of the patient to sodium amytal alone was compared with that to amphetamine sulfate added in different ways on subsequent days, it was apparent that the amphetamine sulfate partially relieved the drowsiness produced by the sodium amytal in both schizophrenic and depressed patients, whereas the psychologic characteristics and the duration of responses differed. For the depressed patients the psychologic characteristics remained unchanged and the duration of the response was increased. For the schizophrenic patients there was a slightly poorer psychologic reaction with no increase in the duration.

The data thus suggested that tolerance[9] to drugs of the barbiturate series may develop more easily in patients with schizophrenia than in patients with depressions. This hypothesis was further supported by the observed phenomenon that subsequent responses to sodium amytal alone in schizophrenic patients often become poorer—indeed, sometimes they fail to appear at all.[3] The present study was therefore designed to answer the question: Do schizophrenic and depressed patients show a similarity or a difference in the development of tolerance to a combination of sodium amytal and amphetamine sulfate?

From the Iowa State Psychopathic Hospital and the State University of Iowa College of Medicine.

1. Berrington, W. P.: Psycho-Pharmacologic Study of Schizophrenia, with Particular Reference to Mode of Action of Cardiazol, Sodium Amytal and Alcohol in Schizophrenic Stupor, J. Ment. Sc. **85**:406 (May) 1939. Sullivan, D. J.: Psychiatric Uses of Intravenous Sodium Amytal, Am. J. Psychiat. **99**:411 (Nov.) 1942.

2. Wagner, C. P.: Pharmacological Action of the Barbiturates: Their Use in Neuropsychiatric Conditions, J. A. M. A. **101**:1787 (Dec. 2) 1933. Longpre, F.: Sodium Amytal Combined with Psychotherapy in Non-Cooperative and Cataleptic Patients, Massachusetts Department of Mental Health, Symposium on Therapy, September 1939, p. 5.

3. Gottlieb, J. S., and Hope, J. M.: Prognostic Value of Intravenous Administration of Sodium Amytal in Cases of Schizophrenia, Arch. Neurol. & Psychiat. **46**:86 (July) 1941.

4. Layman, J. W.: A Quantitative Study of Certain Changes in Schizophrenic Patients Under the Influence of Sodium Amytal, J. Gen. Psychol. **22**:67 (Jan.) 1940.

5. Broder, S. B.: Therapy in Catatonia: Effects of Combining Caffeine Sodium Benzoate with Sodium Amytal, Am. J. Psychiat. **93**:957 (Jan.) 1937.

6. Reitman, F.: Some Observations on Sodium Amytal Experiments: Preliminary Report, J. Ment. Sc. **87**:96 (Jan.) 1941.

7. Myerson, A.: The Reciprocal Pharmacological Effects of Amphetamine (Benzedrine) Sulfate and the Barbiturates, New England J. Med. **221**:561 (Oct. 12) 1939. Myerson, A.; Roman, J.; Rinkel, M., and Lesses, M. F.: The Effect of Amphetamine (Benzedrine) Sulfate and Paradrine Hydrobromide on Sodium Amytal Narcosis, ibid. **221**:1015 (Dec. 28) 1939.

8. Gottlieb, J. S., and Coburn, F. E.: Psychopharmacologic Study of Schizophrenia and Depressions: Intravenous Administration of Sodium Amytal and Amphetamine Sulfate Separately and in Various Combinations, Arch. Neurol. & Psychiat. **51**:260 (March) 1944.

9. The word tolerance as used in this report refers to the psychologic, and not the hypnotic, effects.

## METHOD

Twenty consecutive patients who were suitable for testing, 10 of whom had schizophrenia and 10 depressions, were subjected to a routine procedure. Suitability for testing depended on each patient's meeting four requirements: (1) The patient must present typical signs and symptoms of one or the other disorder; (2) he must not have been taking barbiturates for some time before admission; (3) he must not have previously been subjected to any of the shock therapies (insulin, metrazol or electric), (4) and the duration of the initial response to sodium amytal must be measurable by means of clinical observation. Although the last requirement was necessary in planning the procedure, it operated in a selective way on the two patient populations. Of the patients suffering from a depression and meeting the first three requirements, all but 1 had a response to sodium amytal the duration of which was measurable. This was not true for the schizophrenic patients. It required the testing of 22 patients in order to select 10 with suitable responses for the purposes of this study. Actually, then, the comparison was between unselected depressed patients and the better reactors in the schizophrenic group.

On ten consecutive days, after breakfast, each patient was given an intravenous injection of 250 mg. of sodium amytal followed by 20 mg. of amphetamine sulfate. If the type of response became consistently poor and was unmeasurable for three consecutive days, the series of injections was discontinued. The type and duration of the response and the degree of narcosis were noted. The initial drowsiness which occurred on some occasions did not last longer than fifteen to thirty minutes and presented no complication. The duration of the response was determined to the nearest half-hour, its termination being judged by the clinical observation of the patient, that is, when the behavior had returned to the preinjection level.

"The reactions were evaluated as good, moderately good and poor. For the patient with schizophrenia, a good reaction was defined as one in which the affect was warm and appropriate to the thought content, the associations normal and the insight good as far as the patient recognized that he was ill. A moderately good reaction was defined as improvement in affect, associations and insight with persisting evidence of abnormalities. A poor reaction was defined as considerable defect in affect and thinking or as failure to respond.

"For the patient with a depression a good reaction was defined as a shift of the affective state to or nearly to the normal level and, at the same time, disappearance of all evidence of retardation or agitation, whichever was present. A moderately good reaction was one in which there were definite improvement in the affective state and diminution of retardation or agitation but abnormalities were still evident. A poor reaction was characterized by no improvement in any of the symptoms or by complete failure to respond." [8] In some instances the symptoms became more florid but did not seem to shift toward the normal. Symptoms specific to the drug but not to the illness, such as complaints of light-headedness, dizziness, blurring of vision, numbness and weakness of the extremities and signs of ataxia, nystagmus and vertigo, were disregarded.

## RESULTS

In table 1 are presented the duration and type of responses elicited by 250 mg. of sodium amytal followed by 20 mg. of amphetamine sulfate in the 10 schizophrenic patients for ten or less consecutive days. The injections were discontinued after three consecutive poor, unmeasurable, responses. There was a pronounced consistency in both the type and the duration of responses from patient to patient. Each patient, with 1 exception, had his best type of response to the first injection. Each, with 1 exception, had his longest duration of response to the first injection. Each quickly acquired a poor, unmeasurable, response. These poor responses were characterized at the most by varying degrees of drowsiness. Moreover, there occurred a significant correlation between the type and the duration of the responses. There were 3 good responses, with an average duration of three and five-tenths hours; 22 moderately good responses, with an average of two and four-tenths hours, and 55 poor responses, with an average of five-tenths hour. A level of statistical confidence of 0.1 per cent was obtained for the differences between the durations of the moderately good reactions and the durations of the poor reactions on employing the critical ratio technic. This indicated that the durations of the moderately good reactions were significantly longer than the durations of the poor reactions; hence the implication, the better the type of response the longer is its duration.

The means for the durations reflect the consistency of these changes: The mean initial response was three and three-tenths hours and diminished to zero hours by the eighth day.

The changes in both the type and the duration of reaction for the schizophrenic patients become of considerable significance when contrasted with the observations obtained with the depressed patients. In table 2 are presented the duration and the type of responses elicited by 250 mg. of sodium amytal followed by 20 mg. of amphetamine sulfate in the 10 depressed patients for ten consecutive days. The constancy of the type of response may be evaluated by considering each patient separately. It may then be noted that there were two trends. Patients 1, 2, 3 and 6 maintained approximately the same clinical response in terms of behavioral characteristics for the ten consecutive days. The other 6 patients, however, showed day to day variations—patients 8 and 9 relatively little and patients 4, 5, 7 and 10 considerable variability. When the durations of the responses were examined, considerable variability was also apparent, as indicated by the standard deviations for each patient. Patients 1, 3, 6, 7, 9 and 10 had relatively less variability and patients 2, 4, 5 and 8 relatively more. There was a correlation between the type and the dura-

TABLE 1.—*Responses of Patients with Schizophrenia for Ten Consecutive Days or Less to Injections of 250 Mg. of Sodium Amytal Followed by Injections of 20 Mg. of Amphetamine Sulfate*

| Patient No. | Type of Schizophrenia | First Day | | Second Day | | Third Day | | Fourth Day | | Fifth Day | | Sixth Day | | Seventh Day | | Eighth Day | | Ninth Day | | Tenth Day | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Response* | Duration, Hr. | Response | Duration, Hr. | Response | Duration, Hr. | Response | Duration, Hr. | Response | Duration, Hr. | Response | Duration, Hr. | Response | Duration, Hr. | Response | Duration, Hr. | Response | Duration, Hr. | Response | Duration, Hr. |
| 1 | Undifferentiated | G | 5 | M | 4 | P | 1 | P | 0 | P | 1.5 | P | 0 | P | 0 | | | | | | |
| 2 | Catatonic | M | 2.5 | M | 1.5 | P | 5 | P | 0 | P | 0 | P | 0 | | | | | | | | |
| 3 | Hebephrenic | G | 3.5 | G | 2 | M | 1.5 | M | 1.5 | P | 0.5 | P | 0 | P | 0 | P | 0 | | | | |
| 4 | Catatonic | P | 3 | M | 3 | M | 1.5 | P | 1 | P | 1 | P | 0.5 | P | 0.5 | P | 0 | P | 0 | P | 0 |
| 5 | Hebephrenic | M | 2 | M | 1.5 | P | 1 | P | 1 | P | 0.5 | P | 0.5 | P | 0 | P | 0 | P | 0 | | |
| 6 | Undifferentiated | M | 9 | M | 4 | M | 5.5 | P | 1.5 | P | 0 | P | 3 | P | 4 | P | 0 | P | 0 | P | 0 |
| 7 | Paranoid | M | 2.5 | M | 3 | P | 1 | P | 1 | P | 0 | P | 1.5 | P | 0 | P | 0 | P | 0 | | |
| 8 | Catatonic | M | 1.5 | M | 1 | M | 1.5 | P | 0.5 | P | 0.5 | P | 0.5 | P | 0 | P | 0 | P | 0 | | |
| 9 | Paranoid | M | 2 | M | 0.5 | P | 0 | P | 0 | P | 0.5 | P | 0 | P | 0 | | | | | | |
| 10 | Hebephrenic | M | 2.5 | M | 1 | M | 0.5 | P | 0.5 | P | 0 | P | 0 | P | 0 | | | | | | |
| | Mean | | 3.35 | | 2.15 | | 1.85 | | 0.7 | | 0.45 | | 0.6 | | 0.45 | | 0 | | 0 | | 0 |
| | Standard deviation | | 2.1 | | 1.2 | | 1.8 | | 0.5 | | 0.2 | | 0.9 | | 1.4 | | | | | | |

* G indicates a good reaction; M, a moderately good reaction, and P, a poor reaction.



TABLE 2.—*Responses of Patients with Pathologic Depressions for Ten Consecutive Days to Injections of 250 Mg. of Sodium Amytal Followed by 20 Mg. of Amphetamine Sulfate*

| Patient No. | Diagnosis* | First Day | | Second Day | | Third Day | | Fourth Day | | Fifth Day | | Sixth Day | | Seventh Day | | Eighth Day | | Ninth Day | | Tenth Day | | Mean | Standard Deviation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Response† | Duration, Hr. | Response | Duration, Hr. | Response | Duration, Hr. | Response | Duration, Hr. | Response | Duration, Hr. | Response | Duration, Hr. | Response | Duration, Hr. | Response | Duration, Hr. | Response | Duration, Hr. | Response | Duration, Hr. | | |
| 1 | I. M. | M | 4 | M | 2.5 | M | 3 | M | 6.5 | M | 7 | M | 3.5 | M | 5 | M | 4 | M | 2 | M | 7 | 4.4 | 1.7 |
| 2 | M. D. M. | G | 12 | G | 6.5 | G | 8.5 | G | 5 | G | 1.5 | G | 3.5 | G | 4 | G | 5.5 | G | 12 | G | 3.5 | 6.2 | 3.4 |
| 3 | M. D. M. | M | 3 | M | 7 | M | 5 | M | 2.5 | M | 4 | M | 3 | M | 1.5 | M | 2 | M | 1 | M | 1 | 3.0 | 1.8 |
| 4 | M. D. D. | G | 12 | P | 6.5 | P | 2 | M | 2 | P | 1 | M | 1 | M | 2 | M | 0.5 | M | 1.5 | P | 2.5 | 3.1 | 3.4 |
| 5 | I. M. | P | 12 | P | 3 | M | 8 | M | 8 | G | 7 | M | 5 | P | 2 | P | 1 | P | 4.5 | P | 1 | 5.1 | 3.4 |
| 6 | M. D. D. | M | 2 | M | 4 | M | 5.5 | M | 4.5 | M | 4 | M | 3.5 | M | 3.5 | M | 4 | M | 5 | M | 4.5 | 4.0 | 0.9 |
| 7 | M. D. M. | M | 8 | G | 6.5 | M | 8 | M | 6.5 | M | 8.5 | G | 9 | G | 8.5 | M | 6 | G | 5 | M | 9.5 | 7.5 | 1.4 |
| 8 | M. D. M. | G | 5 | M | 2.5 | M | 5.5 | M | 5 | M | 10.5 | M | 10 | M | 11.5 | M | 9 | M | 8 | M | 8.5 | 7.5 | 2.8 |
| 9 | M. D. D. | M | 5 | G | 2 | G | 3 | M | 3.5 | M | 2.5 | M | 3.5 | M | 2.5 | M | 3 | M | 2 | M | 2 | 2.9 | 0.9 |
| 10 | M. D. D. | P | 5 | P | 1 | M | 1.5 | M | 3 | M | 2 | M | 2 | G | 1.5 | G | 3 | G | 4.5 | G | 4.5 | 2.8 | 1.2 |
| | Mean | | 6.8 | | 4.1 | | 5.0 | | 4.6 | | 4.8 | | 4.4 | | 4.2 | | 3.8 | | 4.5 | | 4.4 | | |
| | Standard deviation | | 3.7 | | 2.1 | | 2.4 | | 1.8 | | 3.1 | | 2.7 | | 3.1 | | 2.4 | | 3.2 | | 2.9 | | |

* I. M. indicates involutional melancholia; M. D. D., manic-depressive psychosis, depressive type, and M. D. M. (manic-depressive psychosis, mixed (agitated depressive) type.
† G indicates a good reaction; M, a moderately good reaction, and P, a poor reaction.

tion of the responses. There were 23 good responses, with an average duration of five and eight-tenths hours; 65 moderately good responses, with an average of four and five-tenths hours, and 12 poor responses, with an average of three and five-tenths hours. A level of statistical confidence of 3 per cent was obtained for the differences between the durations of both the moderately good and the poor reactions and the durations of the good responses on employing the critical ratio technic. There was, however, no statistically significant difference when the durations of the moderately good responses were compared with the durations of the poor responses. Hence, one may conclude that the durations of the good responses were significantly and consistently longer than those of the moderately good or the poor responses.[10]

Yet, in spite of the individual variation in type and duration of responses among the depressed patients, the basic trends of this group contrast sharply with those of the schizophrenic patients. The means for the durations of responses for the depressed patients reflect this contrast: The mean duration of initial response was six and eight-tenths hours, which fell to approximately four hours on the second day but then remained at that level, slightly more or less, throughout the period of observation. The depressed patients thus continued to have approximately the same type and duration of response day after day, in contrast to the schizophrenic patients, whose type of response became poorer and whose duration of response became unmeasurable clinically.

## COMMENT

The observations reported in the preceding section more clearly define the differences in responsitivity to the intravenous injection of a subnarcotic dose of sodium amytal between patients suffering from pathologic depressions and patients suffering from schizophrenia. The positive results as reported to date may be summarized. First, whereas almost all patients suffering from depressions had a change in their symptoms as a response to the injection of the drug, only about 50 per cent of the schizophrenic patients showed a psychologic response other than drowsiness. Because drowsiness was sometimes a complication which masked the change in the patient and made evaluation difficult, amphetamine sulfate was added to the sodium amytal. It was then observed that the better reactions were obtained if the amphetamine sulfate was given after the sodium amytal. This led to the second observed difference: The addition of the amphetamine sulfate produced considerable increase in the duration of the response in the depressed patients but failed to produce a similar effect in the schizophrenic patients.[8] The data presented in the preceding section revealed a third consistent difference between the two patient populations: Whereas the depressed patients continued to maintain approximately the same degree of change in their psychologic characteristics and the duration of the response throughout a ten day period, the schizophrenic patients had their greatest response to the initial injection both in change in psychologic characteristics and in duration, subsequent daily injections quickly leading to a response characterized by no change in the clinical symptoms measurable by clinical means, except for drowsiness in some patients.[11]

These enumerated differences clearly indicate that patients with schizophrenia and patients with pathologic depressions have different orders of responsitivity to the injection of these drugs. Psychologically, the drugs may influence in a selective way the personality function of the patient. They may relieve temporarily the internalized stresses producing the malfunctioning of the personality. Evaluations may be made clinically and applied to the understanding of the individual patient. In addition, the method allows more refined avenues for purposes of investigation into the structure, integration and function of the personality of the psychotic patient.[12]

Beside the numerous psychologic problems which may be approached by this means, the differences in the order of the responses produced by these drugs between the two patient groups imply that an explanation may be sought in terms of either or both neurogenic structure and function.

Despite the voluminous investigative work designed to determine the site of action of the

10. The failure to differentiate between the durations of the moderately good and the durations of the poor responses would indicate that our scale for evaluating the reactions in patients with depressions was accurate bidimentionally rather than tridimentionally. Further support was obtained by the 86 per cent consistency between the evaluations of the types of responses at the time of injection of the drugs and a reevaluation obtained by reading the descriptions of the individual responses after all the data had been collected. All difficulties in evaluation were between the moderately good and the poor responses. None involved the good responses.

11. It may be well to point out that, although the responses of these patients became subclinical, more delicate yardsticks may elicit changes in some of them.

12. Huston, P. E., and Singer, M. M.: Effect of Sodium Amytal and Amphetamine Sulfate on Mental Set in Schizophrenia, Arch. Neurol. & Psychiat. **53**: 365 (May) 1945.

barbiturates on the central nervous system, the question is still controversial. Clinically, the narcotizing effect of the barbiturates closely simulates that of physiologic sleep and is interpreted by some observers as evidence of a selective locus of action. In addition, it has been reported not only that patients with chronic encephalitis lethargica show resistance to the drugs but that patients with paralysis agitans show aggravation of their rigidity.[13] Keeser and Keeser[14] reported deposition of the barbiturates in the thalamus and corpus striatum, none being noted in the pons, cerebellum and medulla. Koppanyi, Dille and Krop,[15] however, were unable to confirm this selective distribution of the barbiturates; their data suggested, rather, that these drugs were found in approximately the same concentration throughout the brain. It is well known, however, that the barbiturates antagonize the analeptic effects of ephedrine, amphetamine and picrotoxin, drugs known to act on the brain stem. In support of this view, Leiter and Grinker,[16] in their studies on the reaction to electrical stimulation of the hypothalamus in cats, found that the responses were more readily elicitable under ether than under dial anesthesia. The present consensus, based on the observations of numerous other investigators,[17] seems to be that the barbiturates act more or less selectively on the hypothalamic functions and by means other than a local action.

Irrespective of the locus of action of barbiturates on the brain, there are a number of observations which when integrated suggest a neural hypothesis pertinent to the understanding of the psychotic patient. A number of investigators[18] have shown that sodium amytal produces fast frequencies (beta rhythm) outside the normal range in the electrocortical continuum as measured by the electroencephalograph. Moreover, Brazier and Finesinger[19] stated that there is a gradient of response in sensitivity of the electroencephalogram from the frontal to the occipital area. They thus inferred that the regions of the cerebral cortex which are the most recent in phylogenetic development are the most vulnerable to the action of the drug. Rubin, Malamud and Hope[20] stated that there is a relationship between the frequency of the electrical potentials and the psychologic changes produced by the drug in schizophrenic patients. Those patients who had a good response to sodium amytal also had considerable increase in the frequency of the electric potentials as seen in the electroencephalogram.

If those observations, then, are integrated with the results herein reported, the problem that presents itself is whether the electroencephalogram will reflect the effect on tolerance to sodium amytal of the two groups of psychotic patients. If these relationships hold true, it would substantiate and allow elaboration of the following hypotheses: There exist a deficient and distorted neural function in schizophrenia and a neural function in pathologic depressions of a different order from that in schizophrenia. These problems are at present under investigation.

Further amplification of these hypotheses of neural dysfunction may be sought in terms of distortion of brain metabolism. Quastel,[21] in his review, pointed out that the barbituric acid derivatives inhibit the oxidation in vitro by brain tissue of *d*-glucose lactic acid and pyruvic acid. The exact point of action of these inhibitors has not yet been established, but the evidence indicates that the enzyme affected is either a flavo-

13. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1941.

14. Keeser, E., and Keeser, J.: Ueber die Lokalisation des Veronals, der Phenyläthyl- und Diallylbarbitursaure im Gehirn, Arch. f. exper. Path. u. Pharmakol. **125**:251 (Sept.) 1927.

15. Kopanyi, T.; Dille, J. M., and Krop, S.: Studies on Barbiturates: VIII. Distribution of Barbiturates in the Brain, J. Pharmacol. & Exper. Therap. **52**:121 (Oct.) 1934.

16. Leiter, L., and Grinker, R. R.: Role of the Hypothalamus in Regulation of Blood Pressure: Experimental Studies with Observations on Respiration, Arch. Neurol. & Psychiat. **31**:54 (Jan.) 1934.

17. Masserman, J. H.: Destruction of Hypothalamus in Cats: Effects on Activity of the Central Nervous System and Its Reaction to Sodium Amytal, Arch. Neurol. & Psychiat. **39**:1250 (June) 1938; Effects of Sodium Amytal and Other Drugs on Reactivity of the Hypothalamus of the Cat, ibid. **37**:617 (March) 1937. Feitelberg, S.; Pick, E. P., and von Warsberg, A.: Ueber centrale Wärme-Erzeugung und Hemmung durch aromatische Amine und Acetylcholin, Arch. internat. pharmacodyn. et de thérap. **61**:447 (April 30) 1939. Laidlaw, R. E., and Kennard, M. A.: Effects of Anesthesia on the Blood Supply to the Hypothalamus, Am. J. Physiol. **129**:650 (June) 1940.

18. Cohn, R., and Katzenelbogen, S.: Electroencephalographic Changes Induced by Intravenous Sodium Amytal, Proc. Soc. Exper. Biol. & Med. **49**:560 (April) 1942. Fowler, O. D.: Neurophysiological and Psychological Changes Induced by Certain Drugs: II. Electrocortical Changes, J. Exper. Psychol. **28**:37 (Jan.) 1941.

19. Brazier, M. A. B., and Finesinger, J. E.: Action of Barbiturates on the Cerebral Cortex: Electroencephalographic Studies, Arch. Neurol. & Psychiat. **53**: 51 (Jan.) 1945.

20. Rubin, M. A.; Malamud, W., and Hope, J. W.: The Electroencephalogram and Psychopathological Manifestations in Schizophrenia as Influenced by Drugs, Psychosom. Med. **4**:355 (Oct.) 1942.

21. Quastel, J. H.: Respiration in the Central Nervous System, Physiol. Rev. **19**:135 (April) 1939.

protein, functioning as a link between dehydrogenase and cytochrome, or an unknown component of the cytochrome system. It is suggested that the effect of the narcotic is to diminish the ability of the nerve cells to oxidize pyruvic acid, lactic acid and *d*-glucose. The access or activation of oxygen is unimpaired, as shown by the lack of effect of the narcotic on the oxygenation of sodium succinate or *p*-phenylenediamine.

Since the schizophrenic patient so quickly loses his ability to respond psychologically to repeated injections of sodium amytal, the question arises whether there may not be some preexisting disturbance of the neural metabolism which would be involved in the aforedescribed narcotizing process. The injection of sodium amytal, then, would put additional stress on an already faulty mechanism—hence the responsitivity of the organism would be inadequate.

## SUMMARY

Sodium amytal followed by amphetamine sulfate was administered intravenously on ten consecutive days to 10 patients with schizophrenia and to 10 patients with pathologic depressions.

1. Whereas 10 of 11 depressed patients had reactions that could be evaluated clinically, it required the examination of 22 schizophrenic patients to obtain 10 with initial responses sufficient for clinical evaluation.

2. For the 10 schizophrenic patients, each, with 1 exception, had his best type and longest duration of response to the initial injection of the drugs. The responses rapidly diminished and became clinically unmeasurable by or before the eighth day. A statistically significant correlation was obtained between the types and the durations of the responses: The better the type of response, the longer was its duration.

3. For the 10 depressed patients, there was considerable intraindividual, as well as interindividual, variability in both the type and the duration of response throughout the ten day period; however, the average of the durations remained fairly constant from the second through the tenth day. A statistically significant correlation was obtained between the types and the durations of the responses: The better the type of response, the longer was its duration.

## CONCLUSIONS

Patients with schizophrenia are characterized by reacting to the intravenous administration of subnarcotic doses of sodium amytal and amphetamine sulfate with (*a*) psychologic responses which, in the present study, were clinically measurable in approximately 50 per cent of the group and (*b*) the rapid development of tolerance in terms of type and duration of the psychologic responses. In contrast, patients with pathologic depressions are characterized by reacting to the same drugs with (*a*) psychologic responses which, in the present study, were clinically measurable in approximately 90 per cent of the group and (*b*) absence of rapid development of tolerance in terms of type and duration of the psychologic responses.

Iowa State Psychopathic Hospital.

# LOCALIZING VALUE OF VERTICAL NYSTAGMUS

LIEUTENANT COMMANDER F. H. O'BRIEN (MC), U.S.N.R.
AND
COMMANDER M. B. BENDER, MC(S), U.S.N.R.

Vertical nystagmus has been considered a sign of disease in the upper portion of the brain stem, the midbrain or the pons. Thus, Stengel,[1] in 1935, reported a case of vertical nystagmus in which autopsy revealed an area of softening in the caudal part of the pons. Marburg[2] stated that vertical nystagmus was clinically observed in cases presenting lesions in the region of the colliculi, and Leidler[3] was able experimentally to produce the same phenomenon with lesions in the cranial portion of the vestibular nuclei of rabbits. Spiegel and Scala,[4] working with cats, brought about vertical nystagmus with lesions in the cerebellar vermis. There has recently come under our observation a case in which vertical nystagmus occurred after occlusion of the anterior spinal artery of the medulla.

## REPORT OF A CASE

A 52 year old chief yeoman, U.S.N.R., was admitted to the hospital with the presenting complaint of increasing weakness of his right arm and leg for about one month. During the same time he had experienced some difficulty in speaking and swallowing. About four days before his admission to the hospital, he had been troubled with pain in his chest and a cough productive of rusty sputum and thick mucus.

He appeared to be acutely ill but, although somewhat stuporous, could be aroused, when he responded clearly to questioning.

Neurologic examination revealed flaccid paralysis of the right arm and leg and evident weakness of the opposite extremities. The tendon reflexes on the right side were more pronounced than those on the left. The superficial abdominal reflexes could not be elicited. There was a classic Babinski toe sign on the right, and the left plantar response betrayed extensor elements. There was no facial weakness.

Perception of pinprick and cotton stimuli was diminished on the right side except on the upper part of the face, but including the right side of the chin. The patient failed to recognize common test objects in the right hand and identified them poorly in the left. Position sense was greatly impaired in the fingers and toes on the right side and was only slightly less defective in the toes of the left foot.

The usual point to point tests were inaccurately executed with the left hand, although rapid, rhythmic, alternating movements were fairly well performed.

The eyegrounds were not remarkable. The pupils had, unfortunately, been dilated by the instillation of a mydriatic. The extraocular movements were unimpaired. There was rapid nystagmus in all directions of gaze, specifically on looking to the right and the left and upward and downward.

The palate rose promptly in the midline, and the gag reflex was elicited from both sides of the pharynx. Swallowing was performed against resistance. The sternocleidomastoid and trapezius muscles appeared equally strong on the two sides. The tongue was directed forward on protrusion.

Two days later the patient was found to present paralysis of the left side as well as the right, again except for the face. Both plantar reflexes were of Babinski type.

Sensation was difficult to evaluate, but vibratory sensibility appeared to be lost except over both clavicles. The tongue curled to the left when protruded.

Nystagmus was now present on horizontal gaze, the right component being stronger than the left. Depression of gaze, though well performed in range, was poorly maintained.

The spinal fluid was normal. The Kahn reaction of the blood was negative. The patient died on the sixth day in the hospital, having presented the typical signs of bronchopneumonia.

Autopsy revealed an area of gross softening in the region of the medulla at the level of the inferior olives and the presence of thrombosis of the anterior spinal artery of the medulla.

Microscopically, the damage was most evident at the same level, involving the pyramids and the medial fillets, and to some extent the posterior longitudinal bundle on the side on which the destruction was more apparent (figure).

The series of events following occlusion of the anterior spinal artery of the medulla has been

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

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth in this article are those of the writers and are not to be construed as reflecting the policies of the Navy Department.

1. Stengel, E.: Zur Frage der Herdlokalisation bei spontanem Vertikalnystagmus, Ztschr. f. d. ges. Neurol. u. Psychiat. **153**:417-424, 1935.

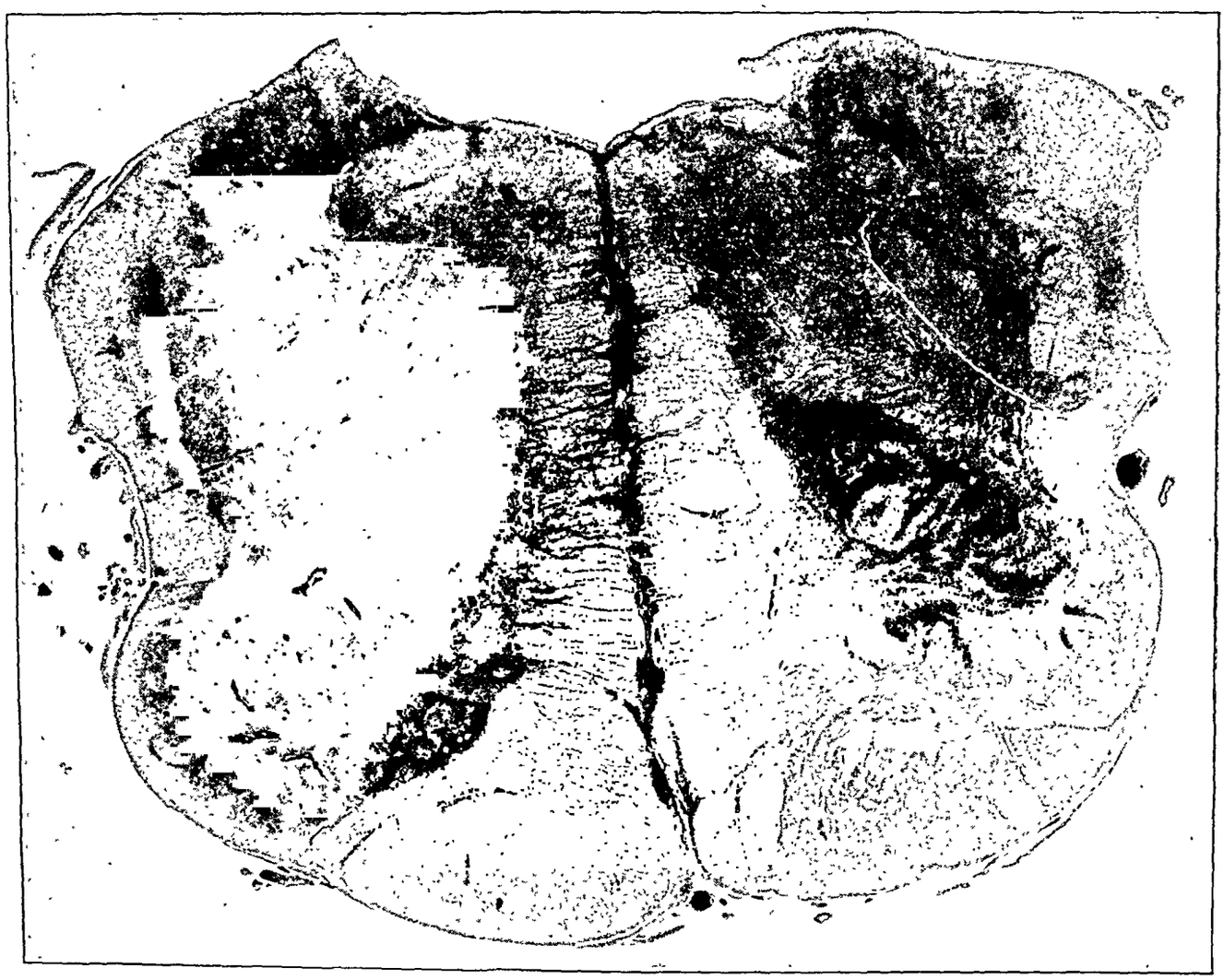
2. Marburg, O.: Modern Views Regarding the Anatomy and Physiology of the Vestibular Tracts, Laryngoscope **49**:631-651, 1939.

3. Leidler, R.: Experimentelle Untersuchungen über das Endigungsgebiet des Nervus vestibularis, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **21**:151-212, 1914.

4. Spiegel, E. A., and Scala, N. P.: Vertical Nystagmus Following Lesions of the Cerebellar Vermis, Arch. Ophth. **26**:661-669 (Oct.) 1941.

emphasized by Davison.[5] As he reported, the lesion is not common, occurring in only 4 of his series of 700 cases of cerebrovascular disease verified at autopsy.

Briefly, the syndrome of occlusion of the anterior spinal artery of the medulla consists in signs and symptoms indicative of loss of function of the pyramidal tract and the posterior column, usually below the head on the side opposite the lesion, and occasionally ipsilateral paralysis of the tongue. Davison noted that in the presence of only one anterior spinal artery, both pyramids and medial lemnisci might be involved, producing sensory and motor loss on both sides. He also reported nystagmus in at least 1 of his cases, stating in effect that in addition to coarse horizontal nystagmus there was variable nystagmus on upward gaze. Thus, here are presented clinicopathologic examples of disease in the medulla producing transient nystagmus in the vertical plane.



Horizontal section of the medulla, showing maximal destruction on the left (at right of photograph), with involvement of the pyramids and the medial lemnisci (distribution of the medullary portion of the anterior spinal artery).

## COMMENT

Evidently, vertical nystagmus may follow on lesions at various levels of the brain stem. Per se the sign cannot be considered indicative of a defect in the midbrain, the pons or the medulla. Its only importance as a clinical sign is its general indication of disease of the brain stem. Leidler [3] attempted to establish direct correlation of vertical nystagmus with lesions in the region of the vestibular nuclei above the level of the abducens nucleus in the rabbit. By producing lesions in the area of the arcuate fibers of the ventrocaudal portion of Deiters' nucleus at the level of the genu of the facial nerve, he obtained horizontal and/or rotatory nystagmus.

This direct relationship of vertical nystagmus to a specific level does not seem to apply either in man or in all experimental animals, for one of us (M. B. B.) has observed in monkeys move-

5. Davison, C.: Syndrome of the Anterior Spinal Artery of the Medulla Oblongata, Arch. Neurol. & Psychiat. **37**:91-107 (Jan.) 1937; Syndrome of the Anterior Spinal Artery of the Medulla Oblongata, J. Neuropath. & Exper. Neurol. **3**:73-80, 1944.

ments of the eyes in the vertical plane produced by stimulation of structures within and immediately ventral to the medial longitudinal fasciculus, even at the level of the hypoglossal nucleus. Moreover, transient upward and downward nystagmus occurred after damage in the same area.[6]

The fact that vertical nystagmus may be seen after lesions at different levels of the brain stem is readily explainable in terms of Lorente de Nó's[7] concept of the vestibulo-ocular system. He pointed out the existence of numerous interrelated neuronal circuits of widespread existence in the brain stem. Thus, a lesion or disturbance which interferes with the functions of these circuits may produce a disorder in ocular movements, such as nystagmus. The type of nystagmus so produced, rotatory, horizontal or vertical, does not depend entirely on the site of the structural defect but is determined by the altered function of the neuronal chain involved.

It is well known that the diagnosis of localization in the brain stem, or indeed of localization anywhere in the nervous system, must ultimately be made by utilization of all the signs present in a given instance. In the case at hand, vertical nystagmus was but one of many signs, and the least significant of all. The neighborhood signs established the level and strongly suggested the nature of the lesion.

## SUMMARY

1. A typical case of thrombosis of the anterior spinal artery of the medulla is reported in which vertical nystagmus was observed.

2. The localizing value of vertical nystagmus is briefly discussed.

3. It is concluded that vertical nystagmus per se is of little localizing value except in so far as clinical experience has shown it to be sometimes seen in cases of disease of the brain stem.

6. These experiments, as yet unpublished, were carried out with the Horsley-Clarke apparatus in collaboration with Capt. E. A. Weinstein, Medical Corps, Army of the United States.

7. Lorente de Nó, R.: The Vestibulo-Ocular Reflex Arc, Arch. Neurol. & Psychiat. **30**:245-291 (Aug.) 1933.

# EMOTIONAL TRAUMA RESULTING FROM ILLEGITIMATE BIRTH

NANDOR FODOR, LL.D.
NEW YORK

For the normal development of a child, the presence of each parent is equally necessary. No man searches more passionately for a dream woman than the child who grows up motherless. The mother is the foundation stone of the world for the infant. A stepmother, nurse or orphanage care never fills the gap which the absence of the mother leaves. However exemplary the manner in which the child's needs are cared for, foster parents and institutions cannot enter into the same psychic bond which the prenatal community of life and immediate postnatal maternal care establish.

While the need for the mother is peremptory and immediate, the father does not enter the child's life until consciousness develops sufficiently for the meaning of home and family to be grasped. When this stage is reached, the absence of the father or suitable father substitutes leaves the child without an important balancing influence. The male parent should be a pillar of strength and a hero ideal for children of both sexes. He should be a god in the infant's universe. His twilight will assuredly come; it is right that it should. But if by brutality the eidolon is shattered prematurely by the father himself, the child's character development may be warped by hatred and fear of the strong parent, and seeds of neurosis may be sown, with the promise of an unwholesome harvest. A boy whose father is cruel may run away from home too soon and vent his hatred on the social order by becoming a criminal or a revolutionary. A girl may develop a masculine character because she has to lean on herself; she may not marry for fear of finding the father duplicated in her husband, and she may be driven to her own sex for the satisfaction of her love needs.

A similar situation to that created by the absence or failure of the parents results from the feeling of not being wanted. The parent who inspires this feeling in the child is guilty of nothing short of a crime. In the world of grown-ups the child is at a natural disadvantage and far too open to adverse suggestions. Because life can be overwhelming, every child needs constant assurance of its own goodness and welcome, or self rejection will follow. The child who has failed to accept itself will grow up with a crippling feeling of inadequacy or, if the environment is conducive to the development of an aggressive character, in open rebellion against society.

In the case of illegitimate birth the child's reactions to life are bound to be completely abnormal. It happens but very seldom that children are left unaware of the stain on the family escutcheon which their very life represents. To be fatherless is hard enough, but to be fatherless with the stigma of illegitimate birth is a psychic catastrophe. It is one of the iniquities of our Western culture that a man may morally fail his child with impunity and that instead of the father we punish the child. It would be far more logical to make the father a social outcast than the child, if we must have a conception of illegitimacy.

## A MODERN LUCIFER

For an abnormal development it is not necessary that the child should be actually illegitimate. The imputation of such illegitimacy produces equally severe psychic scars. I shall illustrate it with leaves from the life of a 40 year old man who came to me for help seven and a half months after a violent attack of schizophrenia.

Ever since the attack he had heard subjective voices from various isolated compartments of his unconscious mind. These voices produced much mental confusion but also answered questions and told surprising stories of their relationship to the total personality.

The patient's dream life appeared to be more or less independent of their influence. The voices developed so much interest in psychoanalysis that the effect often was as if there were several patients on the analytic couch instead of one. They listened with avid interest to the dream revelations and to the interpretation of the symbols used, often trying their own hand at the art.

One day the voices reported that an important message had come through in the patient's dream. This is how they worded it:

"Your mother says you were not wanted. You were brought into this world because she could not help it. You were more trouble to your father and to your mother than you were worth. It is not alone that you were sick at birth and thereafter. Your father thought that some one else had been with your mother. He used to scream at her: 'I would like to kill that s——

of a b—— who slept with you while I was working in the fields to keep the house going.'"

Later, the voices quoted another statement of his father:

"That d— bastard should have died before he was born. . . . I will kill that bastard yet."

The accusation was untrue. The patient grew up in his father's likeness and with many of his character traits. From the age of 4 he was accepted by the father as his legitimate son.

However, the damage was done. Added to it was the fact that because of the father's hostility, and perhaps for many other reasons, the mother's resentment against him was even more serious. The voices claimed that they were aware of her hostility from earliest childhood and that the patient's suicidal compulsion developed under the effect of the mother's constant death wishes against him.

Whether the voices quoted from forgotten memory, telepathic perception or fantasy makes little difference. Their statement was evidence that great harm was done to the patient by the failure of both parents, and this harm had the lion's share in his final psychotic outbreak. According to his own account:

"I went out of my head and wrote to my sister that I was crazy. The voices told me that I was and that they were going to kill me. The Devil offered me unlimited power if I would do his bidding. He said he would give me half of hell to rule over when I died. He would under no conditions let me go to heaven because I knew too much about him and would put him out of business. I was supposed to rule the world and wipe out civilization. There was a new force by which the mind of man could be controlled. It came from another planet, and it manifested itself through me."

Being a bastard (as it was impressed on his infantile mind), he was locked out of the family circle, as Lucifer was cast out of heaven. As Lucifer raged against God and man, so did he, never fully realizing that he wanted to destroy his own father and mother and that God and the world were substitutes on a stupendous scale for the family into which he was born.

The strength of his moral streak kept him from commiting homicide, and by a miracle he escaped being locked up. The voices raved and cursed, impelling him to kill his father and mother and his younger brother, Al. He resisted them. By the time he came to me for help, his homicidal mania had died down, but amazing light was shown on it in retrospect by the dialogue that took place between him and the voices when he was on the analytic couch.

"We did not kill father, did we?" the voice said.

"No, he is still alive," he answered.

"But, Fred, you swore you would kill him!"

"Of course I did, but I was angry then."

I interrupted: "Did you swear to kill Al, too?"

"Did I?" he asked, and the voice answered:

"Yes, you did, once."

"I did not swear that, but I did swear to kill my mother."

"When you swore that, we knew it would not be done. But how could you forgive your father? Can't you remember those things? We have it all here. We hated him."

"I did, too."

"But, Fred, don't you want to kill him now?"

"No."

"We can't understand that. We must give up and realize that those childish things are gone. Fred, we hated him awfully much."

"Yes, we did; but that does not matter now."

"Fred, we don't understand. We hate him here because we have not been told how to stop it. Because we hated father, hatred of Al still stays. We transfer it back and forth. When you worked on Al, we transferred it back to father. How could we but keep it alive? Why don't we kill father? We hate him here. We have never given that up. It is only your conscious mind that has forgiven him. Now what do we do? We told you our fantasies, as you call them. They are real here. We hate him, and we swore we would kill him. Why didn't you shoot him when you had a chance? When you were home at Christmas and saw his gun? Why didn't you do it? Don't you see, Fred, we hate him; God damn it, we hate him! When we cannot hate him, we hate you."

Here was the startling revelation by the inner voice that the hatred of his father, not being allowed a release in a criminal act, turned on him and was destroying the peace of his mind. Now he realized it himself and worded it this way:

"The voices made me my own father. They turned on me to keep the hatred alive."

"Yes, Fred," the voice answered. "We kept up this hatred against you because you would not kill father. We were killing you instead. We wanted him to die in pain. We wanted to chop his head off. We wanted to have his guts out. We wanted to burn him, as he burned Al's hands with a match. Do you remember how he screamed? Fred, would not fire have been a good way to kill him?"

The statement explained a lot of fire fantasies that came out in the patient's dreams.

"We wanted to kill father for beating mother. She was fighting him. We wanted to help her, but you were afraid. He kicked her and hit her, and she kicked him back in the crotch. We did what your mother tried, kick him there. We do that, don't we?"

Here was the explanation of a persistent pain in the testes from which the patient had suffered ever since his psychotic dissociation began. He always ascribed it to the voices, explaining that he was tortured by them. For the first time, the story was out. He suffered the way he wanted his father to suffer. But he suffered on a double score, not only because he had criminal fantasies against his father, but because he refused to yield to them—a truly amazing psychic state.

### POLITICAL CONVERSION

I shall now show the impact of actual illegitimate birth on the dream life of an English woman who, on her mother's side, came from a noble line. She dreamed:

"A Nazi general was walking down the street. I had just read that all our ships were destroyed in the Channel. It was simply terrible. I called to him and asked him if his name was Nègre. He turned round

politely and came back to where I was reading the newspaper. 'Is this you?' I asked, pointing to an article in the *London Times*. I put my right hand on his left sleeve and said: 'Curse you; curse you; curse you!'

"Then he walked away and two women, strangers, came to find out my name. They seemed to belong to this German. They did not believe me when I told my name and looked inside my dress where it was sewn under the left shoulder. They left, and I walked fearfully down the street. I entered an inn and went to the upper floor, looking down from there into the lobby, watching people come and go. Then I came downstairs and went into a room where a venerable bishop was sitting. 'I am afraid the invasion is on,' I said. 'God will protect us,' the bishop replied. A woman sitting near him kissed the ring on his hand.

"I woke up from the dream with the thought: 'I have been disobedient; I ought to have shot the German.' I recalled a statement in the English newspapers that all German soldiers appearing in England must be shot on sight. I thought at the time what a terrible responsibility that was."

I asked the patient for the most emotional element of the dream. She said it was the cursing of the Nazi general. She cursed him three times because everything happened to her in threes. When she was in South America, a man took her for a Nazi sympathizer and proposed a toast to Hitler. She lifted her glass and cursed: "To Hitler; may he rot in Hell!"

Dreams are not influenced by one's political views. Rather are one's political views the result of one's feeling attitude toward people who were in authority over one in childhood. The patient did not know her father, and the stigma of illegitimate birth was rendered heavier by her mother's noble blood and loss of caste on account of her love attachment. It is to be expected that to the unconscious mind of a patient so afflicted, Hitler or a Nazi general or Nazis in general should symbolize the devil father.

In the dream, the patient's concern with names stands out conspicuously. She asked the Nazi general if his name was Nègre, which is "Negro" in French. She obviously was intent on abusing him. By reading the *Times,* she hinted at past times as the source of her hostility. She associated with Negroes blackness and fear, and with French, sexual abnormality. Illegitimacy, by a stretch of imagination, could be considered a sexual abnormality. One can never quite divest one's mind from the notion that birth is a sexual event, and the patient observed that the *Times* is prominently used for birth notices.

I asked her to define cursing. She said it was the refuge of one who is absolutely helpless to do anything else. Cursing thus may well represent an infantile form of self defense.

She discovered in the same breath that the Channel may refer to the uterine passage and that the destruction of ships could represent the danger to her particular ship of life and could stand for the fear of death during the process of birth.

The father, however, is not involved in birth. The cursing is a superimposure, an element regressively associated with birth, an attempt at merging the physical shock with the moral one. She had an excellent motive for such regressive association. Her father did not give her his name; she had no right to it; she was on his "left" side. Left, in dreams, refers to that which is wrong, injurious.

The two women recalled the memory of two women tyrants in her life: her old nurse and the wife of her guardian. As tyrants they well belonged to the Nazi general. She could not remember her answer when the two women asked her name, but as they did not believe her one may assume that she gave her father's name, which she had adopted without legal right. She had this name sewn into her dresses, but not under her shoulder. Under the shoulder is the arm pit, a hairy hollow which has a hidden genital value, by transposition from below to above. In this particular case it was invested with a traumatic significance of its own. Some years before the patient had fallen victim to Yucatan fever, which resulted in semiparalysis of her left arm from the shoulder down. This furnished an excellent background for the psychic paralysis caused by her illegitimacy.

The inn and the upper floor appear to be picturesque allusions to the womb. While she was writing down the dream, the sentence tumbled into the patient's mind: "Jesus entered an inn and went to the upper floor." The association gives this part of the dream a transcendental touch; but as "transcendental" simply means another life, it may as well apply to the Great Before as to the Great Hereafter. The venerable bishop as a symbol of spiritual protection is a good representation of Providence, the good father in heaven, in opposition to the bad father on earth, who forgets to look after his child. No inn can better minister to the needs of its guests than the maternal body to the needs of the child. The invasion was on, and there was death in the Channel; but God's protection did not fail, or the dream would never have been dreamed. However, the Nazi general should have been shot on sight. As the asso-

ciations on awakening are considered part of the dream, the guise of wartime legality openly reveals the dreamer's death wishes against her father, who rendered her illegitimate.

The aggressive emotions revealed by the dream have been stored up in this patient's unconscious mind for half a century. She knew no way of releasing them and was not aware of their destructive character. They redounded on her as they redounded on the psychotic patient, but in a different and very odd form. She fell into her mother's pattern and punished herself for hating her by becoming the mother of an illegitimate child herself.

It is said that the daughters of drunkards almost invariably marry drunkards, even though they had been exposed to a great deal of suffering on their father's account. It would be rather interesting to know what is the percentage of illegitimate motherhood among those who were born illegitimate.

The Park Central Hotel, Seventh Avenue (19).

# EXPERIMENTAL EVIDENCE OF THE PHYSIOLOGIC MECHANISM OF CERTAIN TYPES OF HEADACHE

ARNOLD P. FRIEDMAN, M.D.

CHARLES BRENNER, M.D.

AND

H. HOUSTON MERRITT, M.D.

NEW YORK

In a previous communication,[1] two of us discussed the mechanism of headache produced experimentally by the intravenous injection of histamine, emphasizing the significance of the secondary rise in arterial pressure in the production of the headache. It was found that in patients suffering from post-traumatic headaches such an injection usually "reproduced" the post-traumatic headache (i. e., was followed by a headache which was the same in character and location as the usual post-traumatic one). The conclusion was drawn that the injection of histamine activated a physiologic mechanism similar to that concerned in the production of the majority of post-traumatic headaches.

In the present paper, we wish to report the results of further studies bearing on the mechanism of headaches produced by the intravenous injection of histamine and on the relation between such headaches and various other types of headache encountered clinically. From the facts observed certain conclusions can be drawn about the physiologic mechanism of several types of headache which are met with clinically.

## MATERIAL AND METHOD

The experimental subjects fell into two groups. The first was comprised of patients who had come to the outpatient clinic with the chief complaint of headache. The second was comprised of subjects who had no particular complaint of headache and it included ward patients suffering from a variety of neurologic diseases such as multiple sclerosis, neurosyphilis, amyotrophic lateral sclerosis and peroneal muscular atrophy, as well as young, healthy hospital personnel. For each subject the resting arterial pressure was determined with the subject supine, and 0.1 mg. of histamine base (0.275 mg. of histamine diphosphate) was rapidly injected intravenously. The subject was asked to report anything he felt or tasted and was questioned about his symptoms from time to time. The systolic blood pressure was determined at frequent intervals in most cases for the first two minutes and once or twice thereafter.

In subjects in whom headache developed after the injection, the effects of various special procedures were studied.

The effect of pressure on the carotid artery was investigated by digital compression of one common carotid artery for about fifteen seconds. The test was not considered satisfactory unless pulsation was felt to be absent above the site of compression. After release the subject was questioned about the effect on the headache of both compression and release.

The effect of jugular compression was tested by winding a sphygmomanometer cuff about the neck and inflating it to 25 or 40 mm. of mercury (with 1 subject digital compression was used). The subject was then asked what the effect had been on the headache of both compression and release.

The effect of a second injection of histamine on the headache was tested by injecting a second 0.1 mg. of drug intravenously at the height of the headache.

In one group of subjects the scalp was anesthetized by subcutaneous injection of 25 to 30 cc. of a 2 per cent solution of procaine hydrochloride in a zone lying just above the eyes in front, above the ears laterally and over the occipital protuberance behind. As soon as the scalp thus encircled had become completely anesthetic, the usual intravenous injection of histamine was given and the result noted.

In another group of subjects a painful lump in the scalp was produced by subcutaneous injection of 1 cc. of a 6 per cent solution of sodium chloride. An hour later, after the local pain had disappeared, the subjects received the usual intravenous injection of histamine.[2]

The effect of inhalation of a mixture of 10 per cent carbon dioxide and 90 per cent oxygen on the headache produced by injection of histamine was also investigated. The gas mixture was administered by the usual type of face mask for a period of two minutes, which was sufficient to produce extreme hyperpnea (of maximal depth and with a rate of 35 to 40 per minute). Each experiment began with a two minute period of inhalation. After the respiratory rate had returned to normal, histamine was injected. If headache developed, the patient again inhaled the carbon dioxide–oxygen mixture for two minutes, and the effect of this on the headache was noted. In a few instances the cerebrospinal fluid pressure was measured simultaneously with a lumbar manometer.

This study was aided by a grant from the Lederle Laboratories, Inc.

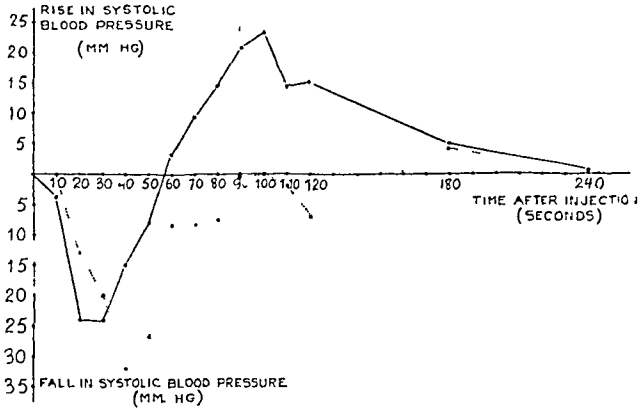
From the Division of Neuropsychiatry, Montefiore Hospital for Chronic Diseases, and the Department of Neurology, Columbia University College of Physicians and Surgeons.

1. Friedman, A. P., and Brenner, C.: Post-Traumatic and Histamine Headache, Arch. Neurol. & Psychiat. **52**:126 (Aug.) 1944.

2. Dr. H. G. Wolff suggested this procedure.

RESULTS

In 31 of 37 patients (38 of 46 injections) in whom the changes in the systolic blood pressure were closely followed, the intravenous injection of 0.1 mg. of histamine base was followed by a headache. In the other 6 patients no headache developed. In the figure the changes in arterial pressures in the two groups of patients are compared. It will be noted that the secondary rise in the group in which headaches developed was about equal to the initial fall (23 and 24 mm. of mercury, respectively), while there was no secondary rise in the group in which headache failed to develop.




Changes in systolic blood pressure following intravenous injection of 0.1 mg. histamine base (0.275 mg. histamine diphosphate). The solid line represents average values for 31 patients (38 injections) in whom headache developed after the injection; the dotted line represents values for 6 patients (8 injections) in whom such headache failed to develop.

Unilateral compression of the carotid artery was performed 18 times on 12 patients while they were experiencing experimentally induced headache. In 6 trials the headache disappeared completely during the period of compression, and in 9 trials it became milder. In 2 of the 9 trials the relief was experienced only, or in greater degree, on the side of the compression. In all 15 trials the pain returned when compression was stopped. In the remaining 3 trials compression failed to relieve the headache. In 1 of the patients, however, subsequent compression of the other carotid artery relieved the headache.

A second intravenous injection of 0.1 mg. of histamine base was given to 3 patients two to three minutes after the first. By that time the arterial pressure had returned nearly to normal and the headache was moderately severe. The second injection was followed by the usual prompt fall of arterial pressure, and the headache as promptly disappeared, to return as usual about a minute later, as the arterial pressure once more rose above the resting level.

Jugular compression was performed on 5 patients (7 trials) and failed to produce any change in the headache in any subject.

Nine patients inhaled a mixture of 10 per cent carbon dioxide and 90 per cent oxygen while experiencing headache. Six of these patients experienced no change in the headache during the inhalation. The other 3 patients experienced slight or moderate relief during the inhalation of the mixture. In 2 of these 9 patients and in 1 other who had no headache after the injection of histamine, the cerebrospinal fluid pressure was measured throughout the experiment by lumbar manometer with the patient lying flat on his side. It was found that inhalation of the carbon dioxide–oxygen mixture did not alter the arterial pressure but did raise the cerebrospinal fluid pressure from an average value of 65 mm. to an average value of 500 mm. of water (3 patients; 5 trials). The intravenous injection of 0.1 mg. of histamine in the same 3 patients raised the spinal fluid pressure from an average value of 67 mm. to one of 192 mm. The rise in spinal fluid pressure following injection of histamine was approximately synchronous with the fall in arterial pressure, as previously reported by Pickering.[3]

Complete anesthetization of the scalp by regional block failed to prevent the development of typical headache in 2 patients. One of these patients had had a previous injection of histamine without scalp block, and he reported that the second headache (after anesthetization of the scalp) was worse than the first had been.

Production of a painful lump in the scalp in 3 patients an hour or so before the intravenous injection of histamine did not apparently influence the location of the headache produced by the histamine. None of the 3 patients localized his headache to the region of the lump.

Twenty-two patients were questioned about similarity of the experimentally produced headache to previous headaches they had experienced as regards character and location of the pain. Twelve patients said the two forms were identical in these respects. In many of these patients the initial, painful pounding present during the secondary rise in arterial pressure following the injection bore no particular relation to the patient's usual headaches. However, as this pounding pain subsided, after one to several minutes, the residual pain (usually steady, though often still throbbing in character) was described by the patient as identical with his usual headaches. Two patients described the experimentally produced headaches as distinctly

3. Pickering, G. W.: Experimental Observations on Headache, Brit. M. J. **1**:907 (May 6) 1939.

different from their usual ones, and one was undecided about the similarity. The other 7 patients had no clear memory of previous headaches.

The diagnostic classification into which these 15 patients' usual headaches fall is of interest. Both patients in whom the histamine did not reproduce the usual headache had no evidence of structural or vascular disease to explain their headaches, had many obviously psychoneurotic symptoms (anxiety, phobias, and/or compulsions, and/or hysterical conversion symptoms) and for many years had had recurrent headaches which bore no resemblance to migraine. This type of headache we classify as psychogenic. Five of the 13 patients in whom histamine reproduced the usual headaches fall into the same group. Closely allied to and perhaps indistinguishable from this group is another one of 5 patients who had occasional headaches of nonspecific type (without accompanying structural or vascular disease), usually related to fatigue or emotional stress. One patient had headaches associated with Paget's disease (osteitis deformans) and increased intracranial pressure; 1 had occasional headaches which were always associated with the onset of an acute infection, and 1 had headaches once every two or three months, always on the first day of her menstrual period.

## COMMENT

In most persons the intravenous injection of 0.1 mg. of histamine base (0.275 mg. of histamine diphosphate) is followed in sixty to ninety seconds by a headache which lasts a few minutes. In a previous article [1] two of us (A. P. F. and C. B.) discussed the sequence of physiologic changes following the injection which appear to be responsible for the appearance of headache. Briefly, the changes were these: Within a few seconds after the injection there are pronounced dilatation of the vessels of the upper half of the body, including the intracranial arteries, and a rapid fall in blood pressure (average, 24 mm. of mercury); a compensatory reflex then produces an increase in cardiac rate and a rise in arterial pressure above the resting level which is about equal to the original fall (figure); as the pressure rises above normal the headache begins, is most intense at about the height of the rise and lasts for a few to several minutes after return of the arterial pressure to normal. The headache is presumably due to stretching of the walls of the intracranial arteries, in which pain endings are known to lie, as the relaxed arteries are distended with blood driven in under increasing pressure.[4]

The role of the secondary (reflex) rise in arterial pressure in the production of headache following injection of histamine was emphasized in an earlier publication.[1] The observations here reported support the correctness of this view. In the first place, as shown in the figure, there was no secondary rise in the group of patients in which headache failed to develop. Next a second injection of histamine abolished the headache as long as the blood pressure was low. Finally, reduction of the cerebral circulation by temporarily occluding one carotid artery abolished or relieved the headache in the majority of subjects. The last two observations confirm those made previously by Pickering.[3]

Earlier authors [3] have laid stress on the importance of changes in the cerebrospinal fluid pressure in the genesis of these experimentally produced headaches. It was felt that the fall in spinal fluid pressure to the resting level (which occurred at about the same time as the onset of the headache) deprived the extracerebral arteries of external support and allowed them to be distended more widely, and hence more painfully. In our experiments, however, the average fall in spinal fluid pressure following the injection of histamine was only 125 mm. of water or 9.2 mm. of mercury, which is much smaller than the average secondary rise in arterial pressure (23 mm. of mercury). Moreover, jugular compression failed to relieve the headache in any case, though the degree of compression used was such as ordinarily elevates spinal fluid pressure by 250 to 400 mm. of water (18 to 29 mm. of mercury). Finally, 6 of 9 patients failed to experience any relief of headache by inhaling the carbon dioxide–oxygen mixture, though the spinal fluid pressure was increased by this procedure by an average of 435+ mm. of water (32+ mm. of mercury) without change in intra-arterial pressure. We conclude from these observations that alterations in the degree of support afforded the arterial walls by the external pressure of the cerebrospinal fluid is much less important in the development of headache following the intravenous injection of histamine than are the variations in arterial pressure which follow the injection.

Our previous observations [1] that in a number of patients with localized, unilateral, post-traumatic headache the injection of histamine "reproduced" the customary headache raised the question whether local injury to the scalp might somehow sensitize it to the action of histamine.

4. Schumacher, G. A., and Wolff, H. G.: Experimental Studies on Headache: Contrast of Histamine Headache with Headache of Migraine and that Associated with Hypertension, Arch. Neurol. & Psychiat. **45**:199 (Feb.) 1941. Pickering.[3]

We have found, however, that injury caused by injection of 1 cc. of a hypertonic solution of sodium chloride does not so sensitize the scalp, nor does anesthetization of the scalp by regional block with procaine hydrochloride affect or prevent the production of headache by injection of histamine. These observations substantiate the current view that headache following the intravenous injection of histamine arises from stimulation of pain fibers within rather than outside the skull.

We may now summarize our present understanding of the physiologic mechanism of this type of headache as follows: The pain arises from stimulation of pain endings (or fibers) which lie in or near the walls of the intracranial arteries. Previous authors [4] have concurred in this conclusion. These structures are stimulated mechanically by the distention of the arteries, the degree of which is determined by two factors: the relaxation of the arterial walls and the rise in intra-arterial pressure. The first of these factors is caused directly by the action of histamine, whereas the second is produced by a secondary vasomotor reflex. The support (or lack of it) to the walls of the arteries by the pressure of the cerebrospinal fluid is of relatively slight importance.

The insight afforded by these observations and those of earlier workers into the physiologic mechanism of headache following intravenous injection of histamine is interesting from the point of view of pharmacodynamics alone, but it is also of considerable clinical significance. In a previous report [1] it was suggested that the physiologic mechanism in many cases of post-traumatic headache was probably similar to that of experimental histamine headache. The basis for this hypothesis was the observation that in many patients suffering from post-traumatic headaches the intravenous injection of histamine was followed by a headache which was identical in character and location with the customary ones of which the patient complained. The observations reported here indicate that the same holds true for many patients with psychogenic headaches, for patients with occasional headaches associated with fatigue and for the 1 patient each with menstrual headache, with headaches associated with Paget's disease of the skull and increased intracranial pressure and with headaches associated with the onset of an acute infection.

The hypothesis, therefore, seems justified that the physiologic mechanism in many cases of psychogenic headache associated with fatigue, as well as in many cases of post-traumatic headache, is similar to the mechanism of the headaches produced experimentally by the intravenous injection of histamine, i.e., stimulation of the pain-sensitive structures lying in or near the walls of the intracranial arteries. To avoid any possibility of misunderstanding, it may be emphasized that this hypothesis does not imply that these clinical types of headache are caused by histamine or sensitivity to histamine. In the case of the experimentally produced headaches the pain-sensitive structures are stimulated mechanically as a result of circulatory and vascular changes. Perhaps the same may be true for some or all of the clinically recognized types of headache.

## SUMMARY

A series of subjects comprised of patients with the chief complaint of headache, patients with a variety of organic neurologic diseases unrelated to headache and healthy controls received 0.1 mg. of histamine base (0.275 mg. of histamine diphosphate) by intravenous injection.

The headache which usually follows such an injection appears to be closely dependent on a secondary rise in blood pressure which follows the initial fall, as shown by (*a*) the absence of such a rise in patients in whom headache failed to develop, (*b*) the temporary disappearance or amelioration of the headache caused by compression of the carotid artery and (*c*) the temporary disappearance of the headache following a secondary injection of histamine.

Support (or lack of it) afforded the walls of intracranial arteries by the cerebrospinal fluid pressure seems to play a small part in the production of such headaches, as shown by the absence of improvement during jugular compression or, in most instances, during inhalation of an oxygen-carbon dioxide mixture.

The essential mechanism of experimentally produced histamine headache seems to be the mechanical stimulation of pain-sensitive structures in or near the walls of intracranial arteries, caused by distention of the relaxed walls by blood driven in under increasing pressure.

Twelve of 15 patients stated that the experimentally produced headache was identical with their usual headaches. In 9 of these 12 patients the usual headaches were related to emotional stress or fatigue; in 1, to Paget's disease of the skull with increased intracranial pressure; in 1, to onset of an acute infection, and in 1, to the menses.

Stimulation by whatever mechanism of pain-sensitive structures in or about the walls of the intracranial arteries would seem to be involved in the production of pain in many cases of chronic headache which are frequently met with in the clinic.

Montefiore Hospital for Chronic Diseases.

# UNILATERAL INTERNAL OPHTHALMOPLEGIA: SOLE CLINICAL SIGN IN PATIENT WITH SYPHILITIC MENINGITIS

COMMANDER MEYER A. ZELIGS (MC), U.S.N.R.
AND
LIEUTENANT GERALD F. JOSEPH (MC), U.S.N.R.

The occurrence of any form of internal ophthalmoplegia always arouses the clinical interest and frequently presents itself as a diagnostic challenge to the examiner. It is well known that disturbances of ocular function, especially pupillary, are commonly encountered in patients with syphilitic involvement of the central nervous system. However, the presence of total internal ophthalmoplegia of one eye as the only clinical sign of syphilis of the central nervous system is extremely rare.

A review of the medical literature of the past decade (*Quarterly Cumulative Index Medicus,* 1935-1945) reveals no report in English describing such an occurrence. In 1935 Puglisi-Duranti,[1] a Spanish ophthalmologist, reported a total of 3 cases of internal ophthalmoplegia as an isolated clinical phenomenon. In 1937 he reported 1 additional case.[2] In 2 of these 4 cases the author described syphilis as the underlying cause of the ocular disturbance. The first case was that of an infant in whom the infection was congenital and the ophthalmoplegia was present at birth; the second case was one of acquired syphilis in which the ophthalmoplegia was bilateral. In the third case the ophthalmoplegia was unilateral and, according to the author, was "due to diabetes." In his subsequent report (1937) Puglisi-Duranti [2] described in detail the ophthalmologic, clinical and laboratory observations in a case of unilateral internal ophthalmoplegia. This disorder occurred in a "laborer" 33 years of age who presented himself for examination because of progressive diminution of vision of the right eye. The visual disorder was of six months' duration, and the patient had gradually lost his ability to read with the right eye. Physical and neurologic examination revealed nothing else significant. Wassermann reactions of the blood and the spinal fluid were positive. Two months later ophthalmoscopic examination showed syphilitic chorioretinitis in both eyes. The unilateral ophthalmoplegia was still present and unchanged at that time.

Our purpose in presenting the following case is twofold: (*a*) to bring to the attention of clinicians, especially ophthalmologists and neurologists, the fact that total internal unilateral ophthalmoplegia may be the only presenting sign of syphilitic meningitis, and (*b*) to emphasize the importance of serologic examination of the blood and the spinal fluid whenever pupillary paralysis is encountered for which no obvious cause has been established, such as a history of encephalitis, ocular or intracranial trauma or the recent use of a mydriatic or cycloplegic drug. Such serologic tests should be made despite a negative history of exposure or complete absence of any previous syphilitic manifestations.

## REPORT OF A CASE

D. D., a 25 year old Marine private first class, single, was admitted to the hospital for study on Jan. 6, 1945, because of an enlarged left pupil.

*Present Illness.*—For two weeks before admission to the hospital, the patient had noted blurring of vision in the left eye. About a week before admission he became aware that his left pupil was much larger than the right. No other symptoms or complaints were elicited.

*Past History.*—The patient had an attack of filariasis in December 1944, which was characterized by swelling, redness and aching of the right forearm, with enlargement of the right epitrochlear lymph node. This attack lasted about two weeks, and there had been no recurrence. There was no history of penile, oral or cutaneous lesions. A Kahn test made in February 1942 gave a negative reaction. There was no history of head injury or any acute illness suggestive of involvement of the central nervous system.

*Mental Examination.*—The patient was alert, intelligent, cooperative and affable. The psyche was normal, and he presented no complaints other than the mild disturbance of vision already described.

*Physical Examination.*—The patient was a well developed and well nourished white man. He did not appear ill. The skin and mucous membranes were

From Marine Barracks, Klamath Falls, Ore.

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth in this article are those of the writers and are not to be construed as reflecting the policies of the Navy Department.

1. Puglisi-Duranti, G.: Clinical Study on Internal Ophthalmoplegia, Riv. oto-neuro-oftal. **12**:256 (March-April) 1935.

2. Puglisi-Duranti, G.: Isolated Internal Ophthalmoplegia: Case Study, Boll. d'ocul. **16**:500 (May) 1937.

clear. The heart was normal, and the sounds were regular. The lungs were clear. The abdomen was soft, with no abnormal masses or tenderness. The genitalia were normal. The extremities presented no abnormality.

*Neurologic Examination.*—Both pupils were round and regular. The left pupil was widely dilated (6.5 mm.) and was completely fixed to light and in accommodation. Two drops of a 0.25 per cent solution of physostigmine salicylate produced prompt miosis. The right pupil was of normal size (3 mm.) and reacted well to light and in accommodation. The extraocular movements were full in all directions. There was no ptosis, nystagmus or strabismus. Funduscopic examination revealed an entirely normal condition.

The remainder of the cranial nerves were intact. The motor system was normal. The deep and superficial reflexes were present and of normal intensity; no abnormal reflexes were elicited. Sensation was entirely normal. Station and gait were normal. There was no stiffness of the neck.

*Laboratory Data.*—A Kahn test of the blood made on January 8, and repeated on January 11, gave a 3 plus reaction on both occasions.

Examination of the spinal fluid on January 9 revealed an initial pressure of 150 mm., a final pressure of 120 mm., normal dynamics, 60 cells (lymphocytes) per cubic millimeter, a Kahn reaction of 4 plus, a colloidal gold curve of 1112331000, a total protein of 49 mg. per hundred cubic centimeters and a sugar content of 80 mg. per hundred cubic centimeters.

*Clinical Course.*—The patient was transferred to another naval hospital. The results of studies of the blood and spinal fluid were strongly positive for syphilis. On this examination the spinal fluid contained 62 lymphocytes per cubic millimeter, and the colloidal gold curve was of the "high midzone type." The patient was given a course of 2,400,000 Oxford units of penicillin over a period of seven and one-half days. Three weeks after this treatment the clinical picture and the Kahn reaction of the blood were unchanged; the spinal fluid now showed only 10 lymphocytes per cubic millimeter, the colloidal gold curve was normal, and the Kahn reaction of the spinal fluid was less strongly positive than on the two previous occasions. Approximately seven weeks after completion of the treatment with penicillin, beginning reaction of the left pupil to light and in accommodation and decrease in its size were noted. A second course of 2,400,000 units of penicillin was given about two months after the first. Immediately after completion of this treatment the Kahn reaction of the blood was only slightly positive. The spinal fluid was not again examined.

On April 6, when the patient returned to duty, the pupil reacted nearly normally to light and in accommodation and was almost of the same size as the normal one.[3]

## COMMENT

Syphilis obviously was the specific etiologic agent in this case. However, the pathogenesis of the ophthalmoplegia is not entirely clear, since the precise anatomic site of the lesion may be nuclear, basilar, radicular or of the peripheral neuron (including the ciliary ganglion and the postganglionic fibers). Since no anatomicopathologic study was possible in this case, it is not within the scope of this report to enter into a discussion of the exact nature and localization of the pathologic process which produced the internal ophthalmoplegia. However, certain deductions which lie within the realm of clinical diagnosis are forthcoming. An ocular lesion (ciliary ganglion and iris) is ruled out by the demonstration of a normal pupillary response following the instillation of a miotic drug (2 drops of a 0.25 per cent solution of physostigmine salicylate was sufficient to produce miosis within about twenty minutes). Examination with the slit lamp revealed a normal iris. A basilar lesion (meningeal exudate) appears unlikely in view of the absence of other neurologic signs, particularly external ophthalmoplegia and ptosis. A nuclear or radicular lesion, therefore, seems the most probable, the pathologic process being either vascular or due to primary syphilitic involvement of one of the Edinger-Westphal nuclei.

## SUMMARY

Isolated unilateral ophthalmoplegia may be the only clinical sign in a patient with syphilitic meningitis.

A case history illustrating such an occurrence is presented.

The diagnostic importance of serologic study in cases of unexplained pupillary paralysis is emphasized.

The rapid therapeutic response to penicillin therapy is mentioned.

The probable anatomic site of such a lesion is postulated.

3. Hasenbush, L. L., Lieut. (jg), U. S. Naval Hosp., Astoria, Ore.: Personal communication to the authors.

# ACTION OF ACETYLCHOLINE ON MOTOR CORTEX

## CORRELATION OF EFFECTS OF ACETYLCHOLINE AND EPILEPSY

FRANCIS M. FORSTER, M.D.

PHILADELPHIA

Sjöstrand [1] demonstrated an increase in electrical activity of the cortex on topical application of acetylcholine following previous application of strychnine and physostigmine. Miller, Stavraky and Woonton [2] and Chatfield and Dempsey [3] found that 1 per cent solutions of acetylcholine bromide and chloride, respectively, applied locally to the previously physostigminized cortex produced an increase of electrical activity. Brenner and Merritt [4] confirmed these observations and demonstrated that the cortical application of stronger solutions of acetylcholine chloride without previous physostigminization resulted in electrical discharges. Brenner and Merritt pointed out the similarity of these discharges to those encountered in clinical electroencephalographic studies, more particularly to the types of electrical activity found during grand mal seizures. Because of this similarity of electrical patterns and because the parenteral administration of acetylcholine can produce seizures, Brenner and Merritt suggested that disorders of acetylcholine metabolism may be important in the causation or mechanism of convulsive seizures.

However, before such an important deduction can be made, two further steps are necessary: (1) the correlation of experimental motor seizures with the acetylcholine discharges, and (2) the determination of other neurophysiologic phenomena known to be present in the epileptic cortex. In this investigation the experiments are concerned with the correlation of the motor seizures and acetylcholine discharges.

From the Department of Neurology, Jefferson Medical College.

1. Sjöstrand, T.: Potential Changes in the Cerebral Cortex of the Rabbit Arising from Cellular Activity and the Transmission of Impulses in the White Matter, J. Physiol. **90**:41P-45P, 1937.

2. Miller, F. R.; Stavraky, G. W., and Woonton, G. A.: Effects of Eserine, Acetylcholine and Atropine on the Electrocorticogram, J. Neurophysiol. **3**:131-138, 1940.

3. Chatfield, P. O., and Dempsey, E. W.: Some Effects of Prostigmine and Acetylcholine on Cortical Potentials, Am. J. Physiol. **135**:633-640, 1942.

4. Brenner, C., and Merritt, H. H.: Effect of Certain Choline Derivatives on Electrical Activity of the Cortex, Arch. Neurol. & Psychiat. **48**:382-395 (Sept.) 1942.

### METHOD

In these experiments 28 cats were employed. All animals were anesthetized by the injection of Dial with Urethane [5] in doses of 0.45 to 0.5 cc. per kilogram of body weight, one-half the dose being administered intraperitoneally and the other half intramuscularly. In studying the results of intracisternal injections of acetylcholine, one hemisphere was exposed over its anterior portion, so that bipolar silver–silver chloride electrodes could be placed over the cruciate gyrus (motor region), and records from the other hemisphere were obtained from steel phonograph needles driven into the intact skull. Acetylcholine chloride was injected intracisternally in amounts varying from 10 to 25 mg. after atropinization of the animals. For detailed studies of the motor cortex, the cruciate gyrus and adjacent areas of one hemisphere were exposed, care being taken to keep bleeding at a minimum. Stimulations were carried out by means of a Harvard inductorium, and bipolar platinum electrodes were used. The motor cortex was explored by stimulation until a region was found yielding a discrete response to stimulation, such as adduction of the shoulder, extension of the paw or flexion of the elbow. Bipolar recordings were obtained from two needles placed in the corresponding muscle. A unipolar silver–silver chloride electrode was placed on the same gyrus within 1.5 mm. of and equidistant from each of the stimulating electrodes. Acetylcholine chloride was applied in 5, 10 or 20 per cent solutions on filter paper pledgets, measuring 1 by 1.5 to 2 mm. These pledgets were carefully dried before application to remove any excess solution and were placed between the stimulating and the recording electrodes. As soon as acetylcholine discharges appeared, the pledgets were removed unless special observations on results of stimulation were to be made. In such instances the pledgets were left in place in order to avoid a complicating factor. All recordings were made by means of a three channel, condenser-coupled amplifier with an ink-writing oscillograph (Grass).

### RESULTS

The intracisternal injection of acetylcholine into the atropinized cat resulted in a depression of electrical activity of the cortex, followed by a long-continued, high voltage, spiking discharge associated with generalized tonic-clonic convulsions. The electrical activity was of the type previously described as acetylcholine discharges. This type of activity was obtained not only from the needle electrodes in the skull but from bipolar silver–silver chloride electrodes over the previously determined motor cortex (fig. 1).

5. Dial With Urethane was supplied by Ciba Pharmaceutical Products, Inc.

Direct application of acetylcholine to the motor cortex, as determined by stimulation studies, was less likely to produce discharges than application to the sensory cortex. Frequently, only a mild increase in electrical activity or scattered spiking occurred, despite the fact that in the same animal applications of acetylcholine to the sensory cortex produced typical discharges, with sharp onset and cessation. In the course of the experiments it was found that the response of the motor cortex to acetylcholine depended in large part on the depth of the anesthesia and the degree of loss of blood during preparation. When due regard was given to these factors and minute pledgets of filter paper moistened with acetylcholine were accurately placed, discharges could be obtained, and these were accompanied with motor evidence of seizures (fig. 2). The electrical discharges were identical with those previously described.[6] The motor component consisted of clonic movements simultaneous with the spiking activity of the cortex. These clonic movements were strictly limited to the muscle group thrown into contraction by electrical stimulation of the same area of cortex. Thus, if acetylcholine was applied to that region of area 4 which on stimulation produced flexion of the contralateral elbow, the clonic movements consisted of repeated flexion and relaxation of the elbow. The seizure did not spread to other portions of the extremity. In some instances in which anesthesia was very light the animal attempted to restrain the convulsing arm by placing the opposite paw on top of it.

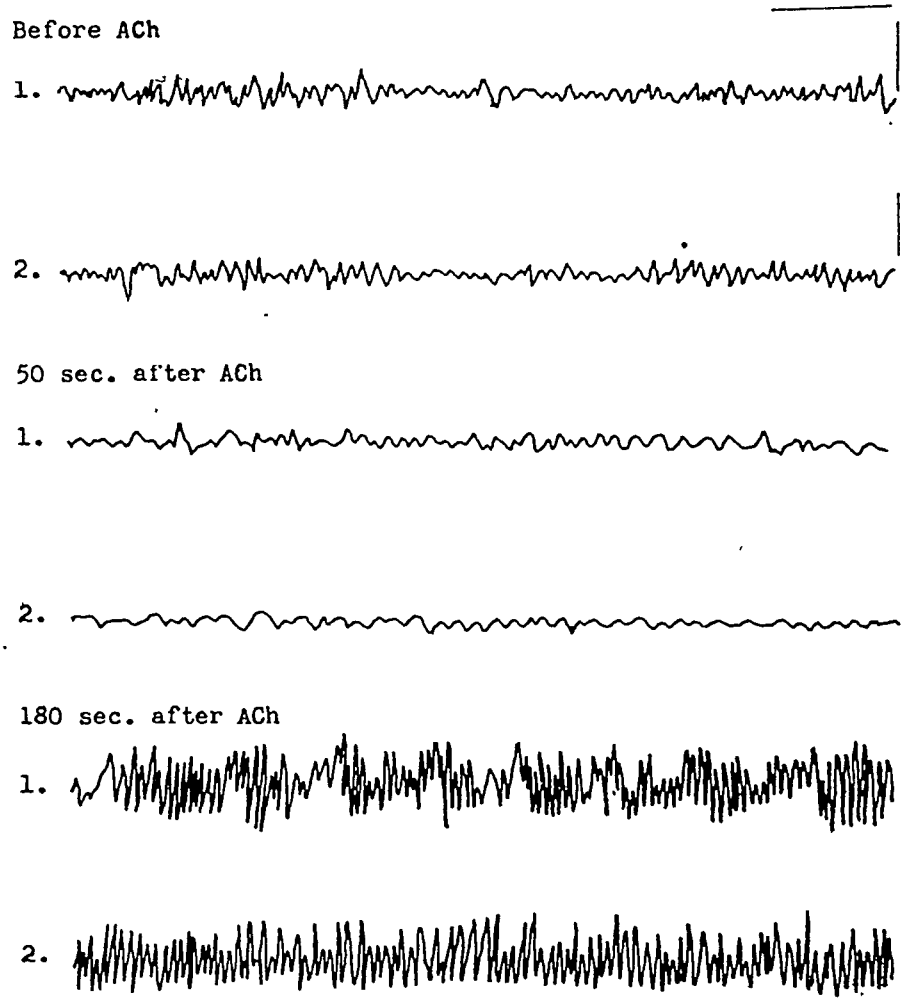



Fig. 1.—Electrocorticograms before and after cisternal injection of acetylcholine. *1* is a record from the right hemisphere through the intact skull; *2*, a bipolar record from the previously explored left motor area.

Within fifty seconds after injection of acetylcholine there was a diminution of electrical activity, followed by rapid, high voltage, spiking discharges from both hemispheres. At the onset of this discharge there were generalized clonic movements of all extremities. The horizontal marker indicates one second; vertical markers indicate 500 microvolts.

Almost immediately after the application of acetylcholine, and before the appearance of the discharges, a depression of the electrical activity

6. (*a*) Forster, F. M., and McCarter, R. H.: Spread of ACh-Induced Electrical Discharges of the Cerebral Cortex, Am. J. Physiol. **144**:168-173, 1945; (*b*) The Effects of Local Application of Acetylcholine to the Acoustic Cortex, J. Neuropath. & Exper. Neurol., to be published. (*c*) Brenner and Merritt.[4]

of the cortex appeared. This was similar to the depression seen on intracisternal injection and to that previously described on application of acetylcholine to the parietal or the auditory receptive area of the cat cortex.[6a,b] This depression of electrical activity was accompanied with decrease or absence of motor response to stimulation. The decrease in stimulability was transient, and its return did not depend on the removal of the pledget. When acetylcholine was placed at a distance, as on the middle suprasylvian gyrus, and a spreading depression of electrical activity was obtained, the motor response to stimulation of the motor cortex also decreased when the electrical activity of the motor area decreased. Strychninization of these distant areas did not in itself produce cortical suppression. During the period of acetylcholine discharges following application of the drug to the motor cortex, the motor response to electrical stimulation of the cortex was frequently enhanced. Usually the responses remained localized to the same muscle group, but the range of movement was increased.

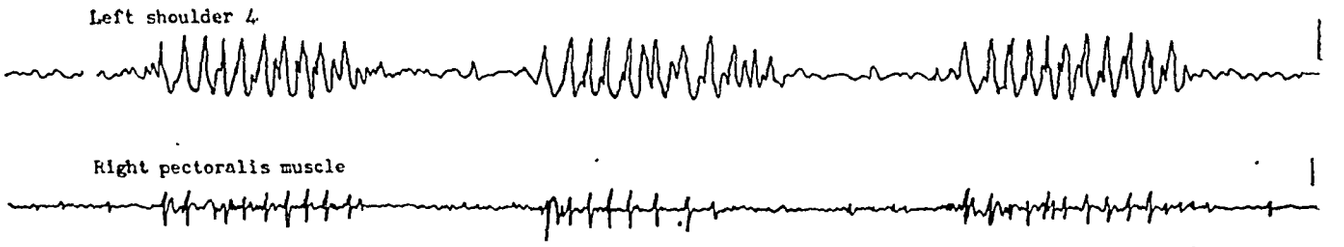



Fig. 2.—Electrocorticogram from the region of the left motor cortex stimulation of which yields discrete contraction of the right pectoralis muscle; electromyogram from the right pectoralis muscle. The record, taken during acetylcholine discharge, demonstrates cortical discharge with simultaneous discharge from muscle. Clonic movements of the right pectoralis muscle were apparent grossly during the recording. The horizontal marker indicates one second; vertical markers indicate 500 microvolts for the electrocorticogram and 200 microvolts for the electromyogram.

## CONCLUSIONS

The convulsive seizures produced in the atropinized cat by the intracisternal injection of acetylcholine are accompanied with electrical discharges of the cerebral cortex of the type previously called acetylcholine discharges.[6a] These discharges can be recorded not only through the intact skull but by bipolar recording from the exposed motor cortex, as previously determined by stimulation.

Under ideal conditions the application of acetylcholine to the motor cortex produces focal clonic convulsions accompanied with acetylcholine discharges. The convulsive movements are sharply limited in scope to the range of movement produced by electrical stimulation of the same region. The ideal conditions necessitate a light state of anesthesia, at least with the type of anesthetic used, and a ready stimulability of the motor cortex. The difficulties in producing motor and electrical discharge by the application of acetylcholine to the motor cortex may depend in large part on the anticonvulsant activities of the anesthetic employed. In any event, there is a sharp difference in the tendency of the motor cortex and that of the sensory cortex to respond with characteristic discharges to topical applications of the drug.

Since the motor discharges are temporarily correlated with the acetylcholine discharges, the application of the drug may be considered responsible for both. The seizures cannot be considered to arise on the basis of the systemic cardiovascular effects of acetylcholine, since atropinization does not prevent their appearance on intracisternal injection and since the motor response to topical application to the motor cortex is focal.

The present contribution therefore links the motor seizure manifestations resulting from applications of acetylcholine with the electrical seizure manifestations. It is safe to say, therefore, that acetylcholine is truly a convulsant, that its activity as such is independent of its systemic action and is therefore a manifestation of its effect on the cerebral cortex and that the acetylcholine discharges are seizure discharges.

In the course of the past few years the role of acetylcholine in neuronal firing has been clarified to some extent. Fulton and Nachmansohn,[7] in a recent review, pointed out the essential role of acetylcholine in the transmission of nerve impulses. Therefore, since acetylcholine is present in nerve tissue, is essential in transmission of nerve impulses and is a convulsant, the possibility is suggested that this substance, its forma-

7. Fulton, J. F., and Nachmansohn, D.: Acetylcholine and the Physiology of the Nervous System, Science **97**:569-571, 1943.

tion and destruction, may play an important, if not the essential, role in the physiologic processes of epilepsy. If this is true, then the cortex treated with acetylcholine should reveal certain neurophysiologic phenomena of the cortex of the epileptic patient, as described by Penfield and his collaborators.[8] These include neuronal transmission of seizure discharges, periods of increased and decreased stimulability and conditioning of the cortex. Forster and McCarter [6a] demonstrated that the spread of acetylcholine discharges is along neuronal pathways, since the spontaneous or induced spread occurs in areas, as demonstrated by strychnine technic, in neuronal continuity with the primary area of application and since interruption of anatomic pathways prevents the spread. Studies of the acoustic cortex by Forster and McCarter [6b] demonstrated sensory precipitation and sensory inhibition of the acetylcholine discharge and periods of decreased and increased auditory stimulability. Sensory precipitation for the somatic sensory cortex has been demonstrated by Chatfield and Dempsey.[3] The role of conditioning of seizure transmission is obviously difficult to determine in acute experiments such as these. In the present studies on the motor cortex, decreased stimulability was found during the periods of depression of electrical activity. This decreased stimulability could not have been the result of a local phenomenon of the motor cortex, and therefore perhaps dependent on the presence of the pledget or of similar artefactual origin, since the stimulability returned to normal despite the continued presence of the pledget and since these alterations of stimulability occurred when the origin of depression was from a distant site, as on the middle suprasylvian gyrus. The application of strychnine to these distant areas without the development of depression of electrical activity or stimulability indicates that the depression did not arise from stimulation of one of the suppressor areas described by Dusser de Barenne and McCulloch,[9] nor was it due to mechanical stimulation of the cortex as described by Leao.[10] Further observations are being made on this depression of electrical activity and cortical function. However, the close relationship between cortical depression and experimental seizure discharges has recently been stressed by Leao.[10] Increased stimulability of the motor cortex has been demonstrated during the period of acetylcholine discharge.

Acetylcholine is therefore a convulsant. It holds the unique distinction among convulsant drugs of being normally present in the cortex. In addition, its presence is integrally related to neuronal firing. Its behavior as a convulsant is similar in its manifestations to that of the cortex of the epileptic patient. The logical deduction from these facts is that acetylcholine plays an important, if not the essential, role in the manifestations of epilepsy. Indeed, abnormalities of acetylcholine metabolism may well be the physiologic cause of epilepsy.

The major objection to this premise is the concentrations of acetylcholine employed in these, and in previous, studies. These concentrations are many times those of the cortex. Even the minimum concentrations effective in producing acetylcholine discharges after previous physostigminization [11] are much greater than the normal quantities. However, this objection need not invalidate the conclusions. Gerard [12] has shown that the isolated frog brain, when immersed for thirty minutes in a 1:100,000 solution of acetylcholine, presents unmistakable evidence of increased electrical activity. Obviously, it is not possible to handle in this manner cortex from which one expects to elicit motor or sensory responses. The discrepancy in effective concentrations may be due to difficulties in penetration of the solution through the intact pia-arachnoid and cortex to the neurons. Another factor is the cholinesterasic activity of the cortex, with rapid destruction of acetylcholine.

## SUMMARY

The electrical discharges of the cortex produced by acetylcholine are similar to seizure discharges. These discharges can be correlated with the motor components of seizures. Variations of cortical stimulability, neuronal transmission of discharges, sensory precipitation and sensory inhibition have been correlated with acetylcholine discharges and epileptic discharges. Because of these observations and the normal presence of acetylcholine in the cortex, the view is taken that acetylcholine plays an essential role in the physiologic genesis of epilepsy.

Jefferson Medical College.

8. (*a*) Penfield, W., and Erickson, T. C.: Epilepsy and Cerebral Localization: A Study of the Mechanism, Treatment and Prevention of Epileptic Seizures, Springfield, Ill., Charles C Thomas, Publisher, 1941, chap. 8, p. 625. (*b*) Penfield, W., and Boldrey, E. B.: Cortical Spread of Epileptic Discharge and the Conditioning Effect of Habitual Seizures, Am. J. Psychiat. **96**:255-281, 1939.

9. Dusser de Barenne, J. G., and McCulloch, W. S.: Factors for Facilitation and Extinction in the Central Nervous System, J. Neurophysiol. **12**:319-355, 1939.

10. Leao, A. A. P.: Spreading Depression of Activity in the Cerebral Cortex, J. Neurophysiol. **7**:359-390, 1944.

11. Sjöstrand.[1] Miller, Stavaky and Woonton.[2]

12. Gerard, R. W.: The Interaction of Neurones, Ohio State J. Sc. **41**:160-172, 1941.

# CHANGES IN CEREBRAL VEINS IN HYPERTENSIVE BRAIN DISEASE AND THEIR RELATION TO CEREBRAL HEMORRHAGE

## CLINICAL PATHOLOGIC STUDY

I. MARK SCHEINKER, M.D.
CINCINNATI

There are few chapters in neuropathology of wider practical interest than that of hypertensive disease of the brain. This is mainly because arterial hypertension is a frequent associate of cerebrovascular accidents. The occurrence of massive hemorrhages in cases of arterial hypertension is familiar to clinicians and pathologists alike. With the exception of ruptured aneurysm, arterial hypertension is the condition most frequently associated with cerebral hemorrhage.

The histologic features of hypertensive disease of the brain have been described in detail.[1] In all cases typical alterations of the arterioles and capillaries were observed, which consisted of hyaline degeneration and fibrotic thickening of the wall and narrowing or complete obliteration of the lumen. It has been emphasized that these arteriolar alterations are different from those found with arteriosclerosis. The alteration of the nerve parenchyma consisted in diffusely scattered, small foci of old and recent softening, secondary to the arteriolar lesions.

While the arteriolar changes associated with hypertension have been relatively well studied, little or no attention has been devoted to the histologic changes in the veins.

This presentation is chiefly concerned with the venous alteration associated with hypertensive disease of the brain, which appears to have escaped much notice, though it is of frequent occurrence. The significance of the venous change in the origin of massive intracerebral hemorrhage is discussed.

### MATERIALS AND METHODS

This presentation is based on a study of 65 typical cases of hypertensive disease of the brain associated with massive cerebral hemorrhage. In 52 cases there were large hemorrhagic cavities filled with blood; in 13 cases only small "ball hemorrhages" were found. The latter were also present in nearly every case of massive intracerebral hemorrhage in this series.

In the past most attention has been given to investigation of the extensive hemorrhagic areas, and attempts have been made to find the ruptured artery. It should be emphasized that in these areas all constituents of the brain parenchyma have been destroyed or secondarily changed by the invasion of large masses of blood. The vascular alterations in these areas cannot, therefore, indicate the preapoplectic state of the blood vessels.

In this study an attempt was made to examine the process in its earliest stages rather than later, when secondary destruction of tissue had occurred. For this purpose, large hemorrhagic lesions were excluded from investigation, and histologic analysis was limited to lesions which have been described as ball hemorrhages *(Kugelblutungen)*. They represent a miniature form of massive hemorrhage, and because of their minuteness they offer a better opportunity for study of the primary vascular alterations.

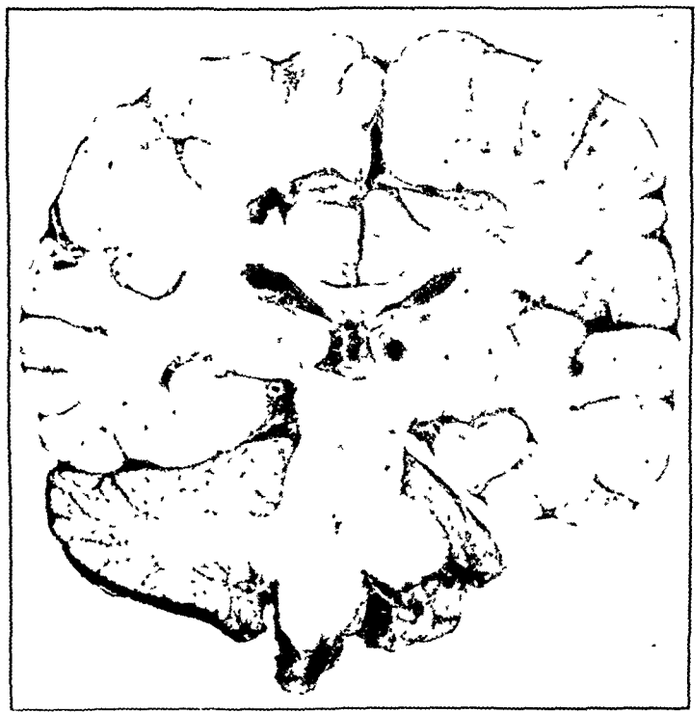


Fig. 1.—Two ball hemorrhages in the left pulvinar region and one in the cortical gray matter of the left parietal lobe.

Numerous sections taken from grossly intact areas of gray and white matter in the vicinity of the larger hemorrhages were also studied.

### OBSERVATIONS

*Ball Hemorrhages.*—The gross changes, which were uniform in character, are well illustrated in

From the Laboratory of Neuropathology, Cincinnati General Hospital and the University of Cincinnati College of Medicine.

1. Scheinker, I. M.: Hypertensive Disease of the Brain, Arch. Path. **36**:289 (Sept.) 1943; Zur Histopathogenese der Hirnapoplexie bei Hypertonie, Monatschr. f. Psychiat. u. Neurol. **102**:158, 1940.

figure 1. Small, round or oval, sharply demarcated hemorrhagic foci could be seen scattered through the gray and white substance of the hemispheres. They varied from 10 to 50 mm. in diameter. In only a few instances could they be found in the vicinity of massive hemorrhages; their site was in areas far remote from the large hemorrhage cavities.

On microscopic examination, the ball hemorrhages, with but few exceptions, were found to consist of one or several blood vessels surrounded by large masses of coagulated blood. These vessels were medium-sized, congested veins, the lumen of which was extremely distended, and far advanced degenerative changes had occurred in the wall. The degree of degeneration is illustrated in figures 2 and 3. The wall of the vein had undergone almost complete degeneration, and the blood within merged with the extravasated blood surrounding it. Some of the veins were surrounded by a zone of infiltration, consisting of white and red blood cells. The venous walls showed almost complete loss of stainability. In relatively few instances had the veins undergone complete disintegration, and then it was difficult to be sure of the source of the hemorrhage. No evidence of rupture of a vessel wall could be found in any of the ball hemorrhages.

The adjacent nerve parenchyma was with but few exceptions found to be fairly well preserved. It showed evidence of compression by the blood clot and an early stage of edema formation (figs. 2 and 3). Beyond this zone of compression there were no signs of preexistent softening or disintegration of tissue.

Fig. 2.—A small central vein in a ball hemorrhage, showing almost complete degeneration and disruption of the vessel wall. Hematoxylin and eosin; × 55.

*Healed Hemorrhages.*—Microscopic studies disclosed numerous foci of glial proliferation in the vicinity of dense accumulations of blood pigment (fig. 4). The central region was composed of amorphous masses of blood pigment. The nerve parenchyma was completely destroyed; it contained no nerve cells or nerve

fibers. The center was surrounded by a transition zone composed of numerous gitter cells packed with blood pigment. The peripheral zone of demarcation consisted of a dense felt-work of glial fibers with glial nuclei. This area of gliosis graded off gradually into normal nerve parenchyma. These represent focal areas of destruction of nerve tissue by a ball hemorrhage, followed by reactive glial change. They may, therefore, be designated as healed hemorrhages.

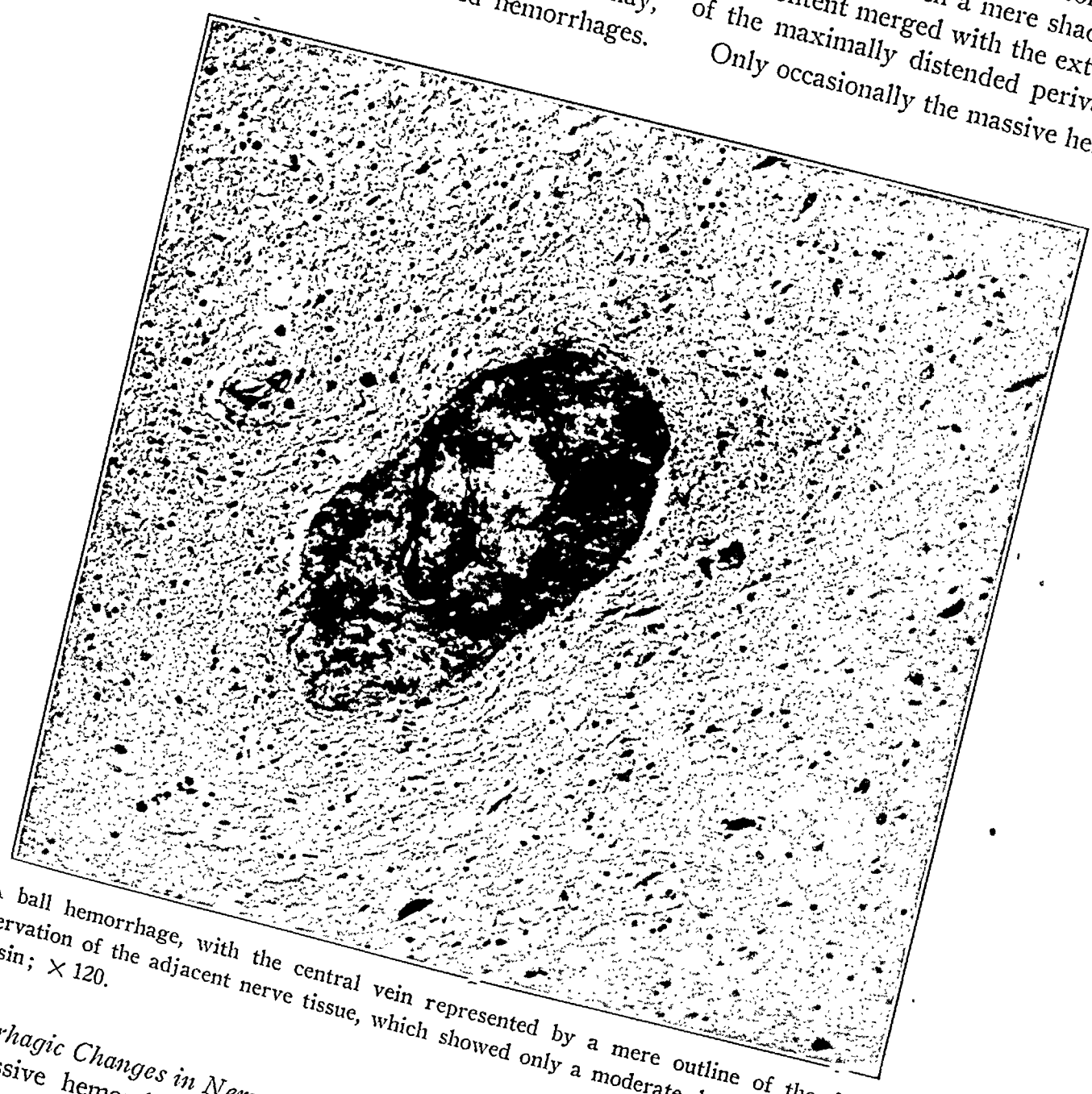


Fig. 3.—A ball hemorrhage, with the central vein represented by a mere outline of the disintegrated wall. Note the preservation of the adjacent nerve tissue, which showed only a moderate degree of compression. Hematoxylin and eosin; × 120.

*Extrahemorrhagic Changes in Nerve Tissue.*— The large massive hemorrhage was, with but few exceptions, surrounded by numerous small perivenous hemorrhages (fig. 5) and by a large zone of advanced edema. The latter was characterized by an areolar, or sievelike, appearance of the tissue, maximal congestion of the smaller veins and capillaries, with distention of the perivascular spaces, and transudation of serous fluid into the nerve parenchyma; the glia displayed clasmatodendrosis and ameboid degeneration. The small perivenous hemorrhages are well illustrated in figure 5. The veins were maximally distended and engorged with blood, displaying signs of stasis; their walls showed extreme thinning and necrosis. In some of the veins there was to be seen a mere shadow of the wall; their content merged with the extravasated blood of the maximally distended perivascular spaces. Only occasionally the massive hemorrhage was found to be surrounded by a narrow zone of encephalomalacia, characterized by complete destruction of tissue and replacement with compound granule cells.

It seems appropriate at this point to indicate in passing some observations described in detail elsewhere. In about two thirds of the cases of massive intracerebral hemorrhage in this series there was associated edema of the brain stem and hemorrhage. The latter was predominantly peri-

venous in distribution and was associated with an extreme degree of venous congestion. Attention has been directed to a clinicopathologic condition described as "transtentorial herniation of the brain stem" responsible for the origin of the hemorrhages of the brain stem.[2]

*Venous Alterations.*—In all cases in which examination was made, the veins, particularly those of the central white matter and of the basal ganglia, showed three types of abnormalities, which were in some cases combined and in others observed separately: (*a*) congestion and stasis, associated with a tremendous distention of the lumen of the vein, (*b*) advanced atrophy, and (*c*) disintegration and necrosis of the wall of the vein.

Venous congestion and stasis were among the most frequently observed changes. Figures 6 and 7 show cerebral veins which display an extreme degree of distention of their lumens and signs of stasis. Their walls disclosed some evidence of degeneration. These relatively early vascular lesions appear to cast light on the pathogenesis of cerebral massive hemorrhage and should therefore be specifically emphasized. Figure 6 shows, in addition to the vascular alteration, the evidence of beginning reaction of the surrounding nerve parenchyma, characterized by rarefaction and an early stage of edema formation. Figure 7 illustrates more advanced changes, characterized by increased permeability of the maximally distended vein for red blood cells and serous fluid, associated with marked degeneration of the wall.

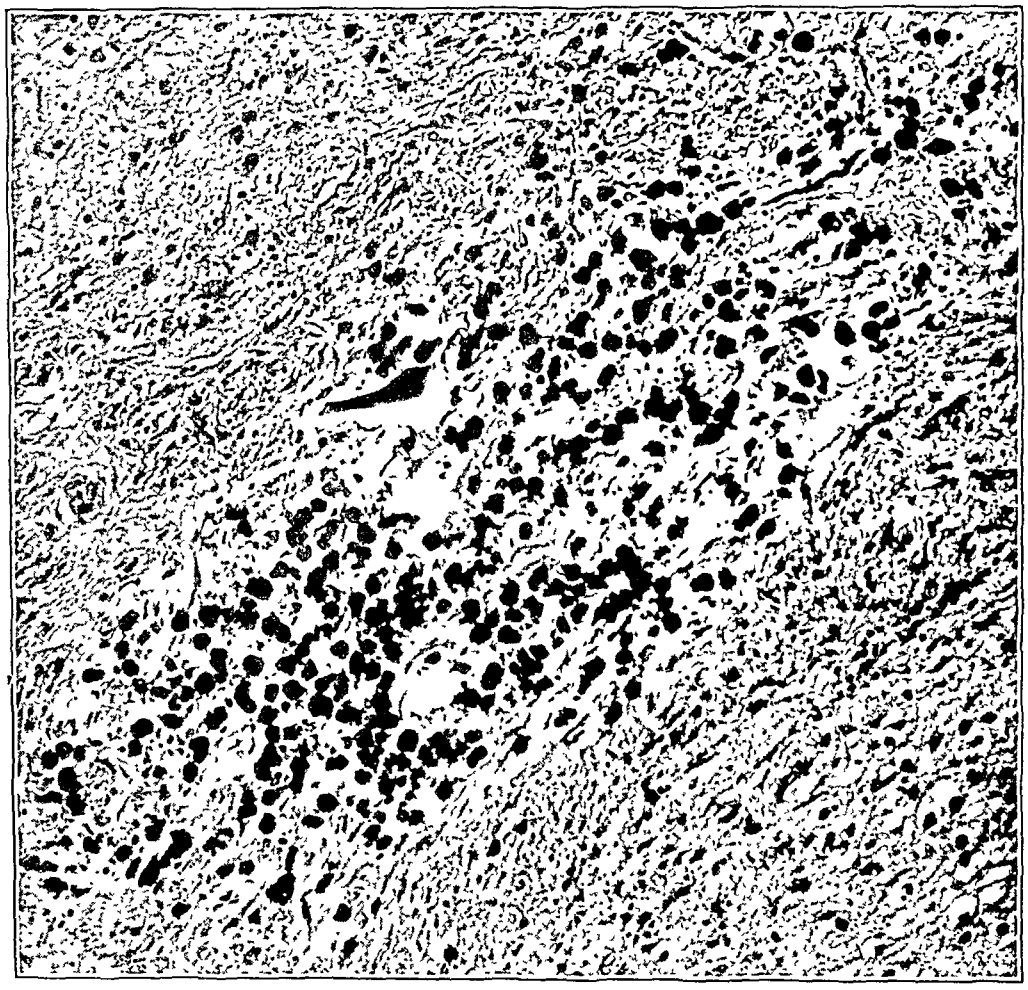


Fig. 4.—Healed hemorrhage, characterized by a focal area of glial scar formation about a dense accumulation of blood pigment. Hematoxylin and eosin; × 160.

Advanced atrophic alteration of the cerebral veins was the rule (figs. 8 and 9). Figure 8 shows in cross section a large vein from the basal ganglia displaying an extreme degree of atrophy. The normal appearance of the division into three coats is completely lost. The entire vessel wall is

2. Scheinker, I. M.: Transtentorial Herniation of the Brain Stem: A Characteristic Clinicopathologic Syndrome; Pathogenesis of Hemorrhages of the Brain Stem, Arch. Neurol. & Psychiat. **53**:289 (April) 1945.

tremendously thinned out and is restricted to a thin connective tissue membrane. It is completely devoid of either muscular or elastic elements. It is bounded on the luminal margin by a few endothelial cells, which are barely visible. The differentiation between endothelial nuclei and those of the surrounding connective tissue membrane is obscured and cannot always be made. The perivascular space is distended and harbors a few nuclei of macrophages.

tureless, homogeneously stained, slightly translucent necrotic ring (fig. 10). It was by no means rare that certain parts of the vessel wall were reduced to an extremely thinned-out membrane, as though on the point of rupture. Cross sections of some of the larger veins revealed completely misshapen and disintegrated walls, bounded exteriorly by accumulations of blood pigment and degenerated, edematous and rarefied nerve tissue (fig. 11). The adventitia was frequently distended with extravasated blood, which

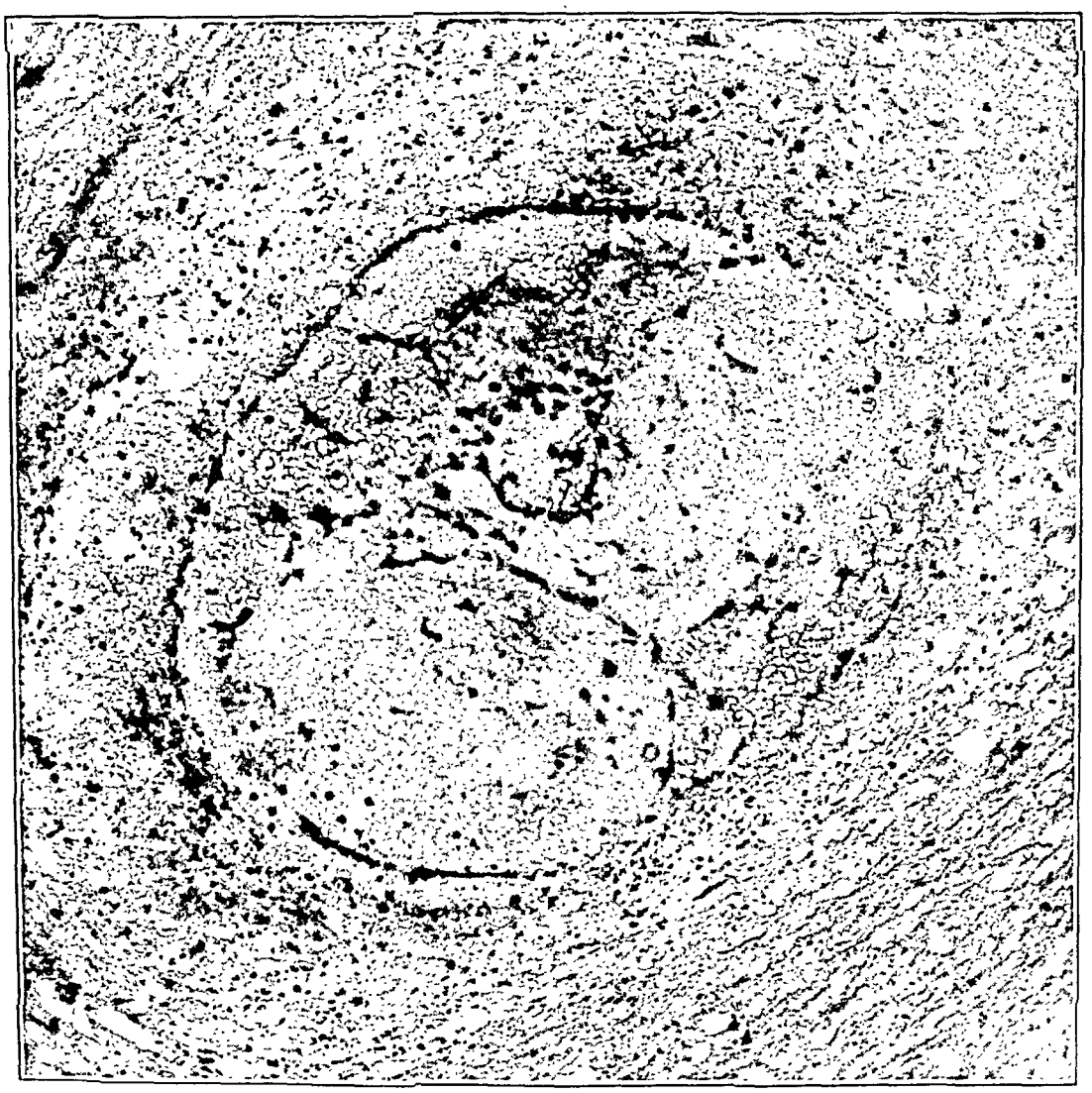


Fig. 5.—Perivenous hemorrhage and edema in the vicinity of a massive hemorrhage. Note the thinning and necrosis of the vessel wall. Hematoxylin and eosin; × 160.

The atrophic changes of the smaller veins (fig. 9) were similar in nature. In contrast to the abnormal thickening of the smaller arterioles, the veins were conspicuously atrophied. Their wall consisted of a simple tube, containing a small quantity of connective tissue fibers and a hardly discernible layer of endothelial cells; there were no muscular or elastic elements.

The atrophic changes of the veins were frequently associated with necrobiotic alterations of the wall (figs. 10 and 11). In many veins the entire wall appeared transformed into a structure at several points appeared to have merged with small hemorrhagic foci of the surrounding nerve parenchyma (fig. 12). Only occasionally were these adventitial changes restricted to one particular segment of the vessel wall, at which point a small extravasation resulted in an aneurysmal dilatation of the adventitia, thus imitating the much disputed, so-called miliary aneurysm described by Charcot and Bouchard [3] as the con-

3. Charcot, J. M., and Bouchard, C.: Nouvelle recherches sur la pathogénie de l'hémorrhagie cérébrale, Arch. de physiol. norm. et path. **1**:110, 643 and 725, 1868.

stant vascular change in brains with massive cerebral hemorrhage. Frequently the perivascular spaces were found to be tremendously distended and torn, permitting the escape of red blood cells and transudation of serous fluid into the surrounding tissue.

## HISTORICAL REVIEW

Cerebral hemorrhage is one of the commonest and least understood pathologic conditions. Many theories have been offered to explain the pathophysiology. Charcot and Bouchard [3] cited "miliary aneurysms," rupture of which they considered to be frequently associated with massive cerebral hemorrhage. Their concept was reflected in many textbooks, though this purely mechanical interpretation of the cerebral hemorrhage raised some objections.

Rosenblath [4] pointed out the frequent coexistence of cerebral hemorrhage and advanced renal disease and expressed the opinion that an enzyme from the kidney might lead to autolysis of nerve tissue, thus creating an area of prehemorrhagic softening predisposed to cerebral hemorrhage.

Westphal and Bär [5] were the first to call attention to the significance of functional vascular disturbances in the pathogenesis of cerebral hemorrhage. They advanced the idea that repeated angiospasm of one or more cerebral vessels was the probable cause of local ischemic changes in the nerve parenchyma. With the relief of spasm, the reopened blood vessel no longer had the support of a wall of firm brain parenchyma and hemorrhage might result.

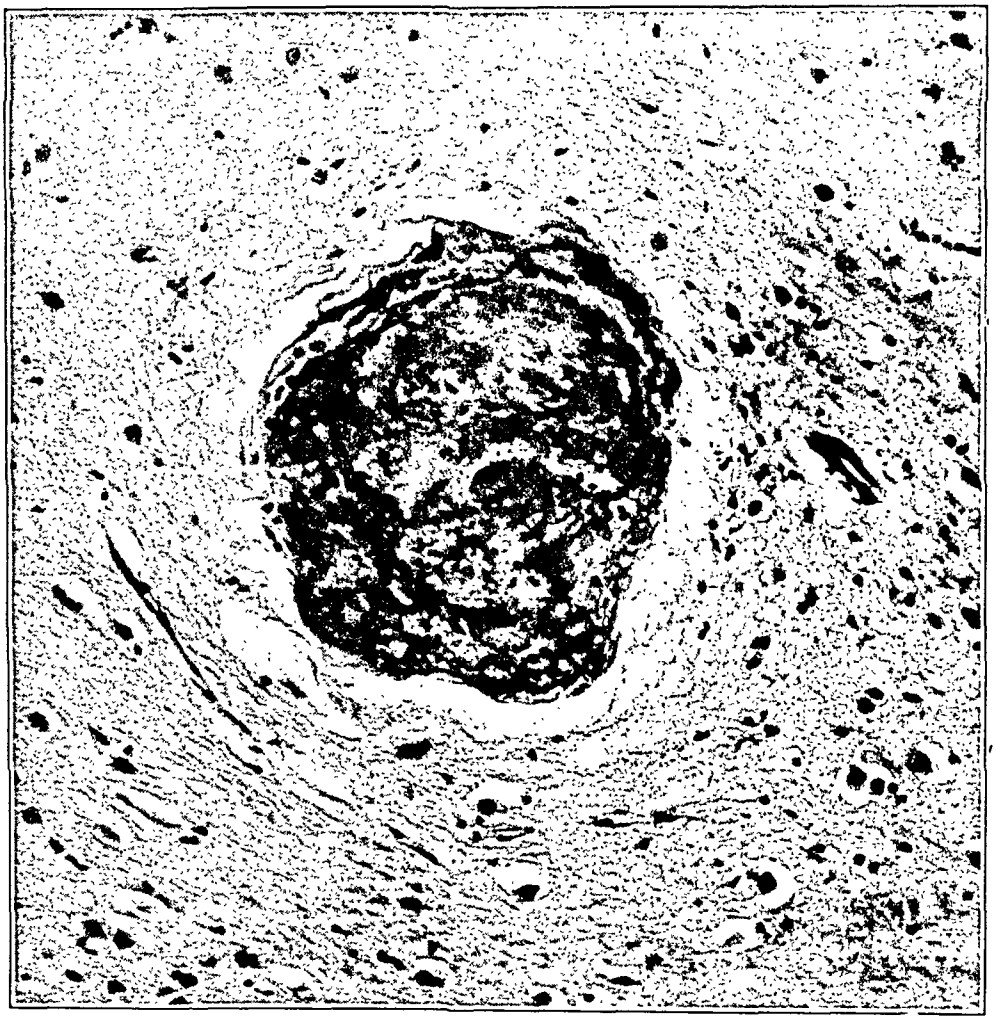


Fig. 6.—Extreme degree of venous congestion and stasis associated with partial disintegration of the wall. Note the rarefaction and edema of the surrounding tissue. Hematoxylin and eosin; × 160.

4. Rosenblath: Ueber die Entstehung der Hirnblutung bei dem Schlaganfall, Deutsche Ztschr. f. Nervenh. **61**:10, 1918.

5. Westphal, K., and Bär, R.: Ueber die Entstehung des Schlaganfalles, Deutsches Arch. f. klin. Med. **151**:1, 1926.

Schwartz,[6] basing his opinion on the experimental observations of Ricker,[7] expressed the belief that all embolic, arteriosclerotic and hypertensive hemorrhagic lesions are morphologic expressions of a common physiopathologic process. He stated the opinion that injury to nerve tissue is secondary to local circulatory disturbances, which may result from many irritants, and that these disturbances may be transmitted to remote areas of the brain by the nervous mechanism of the blood vessels.

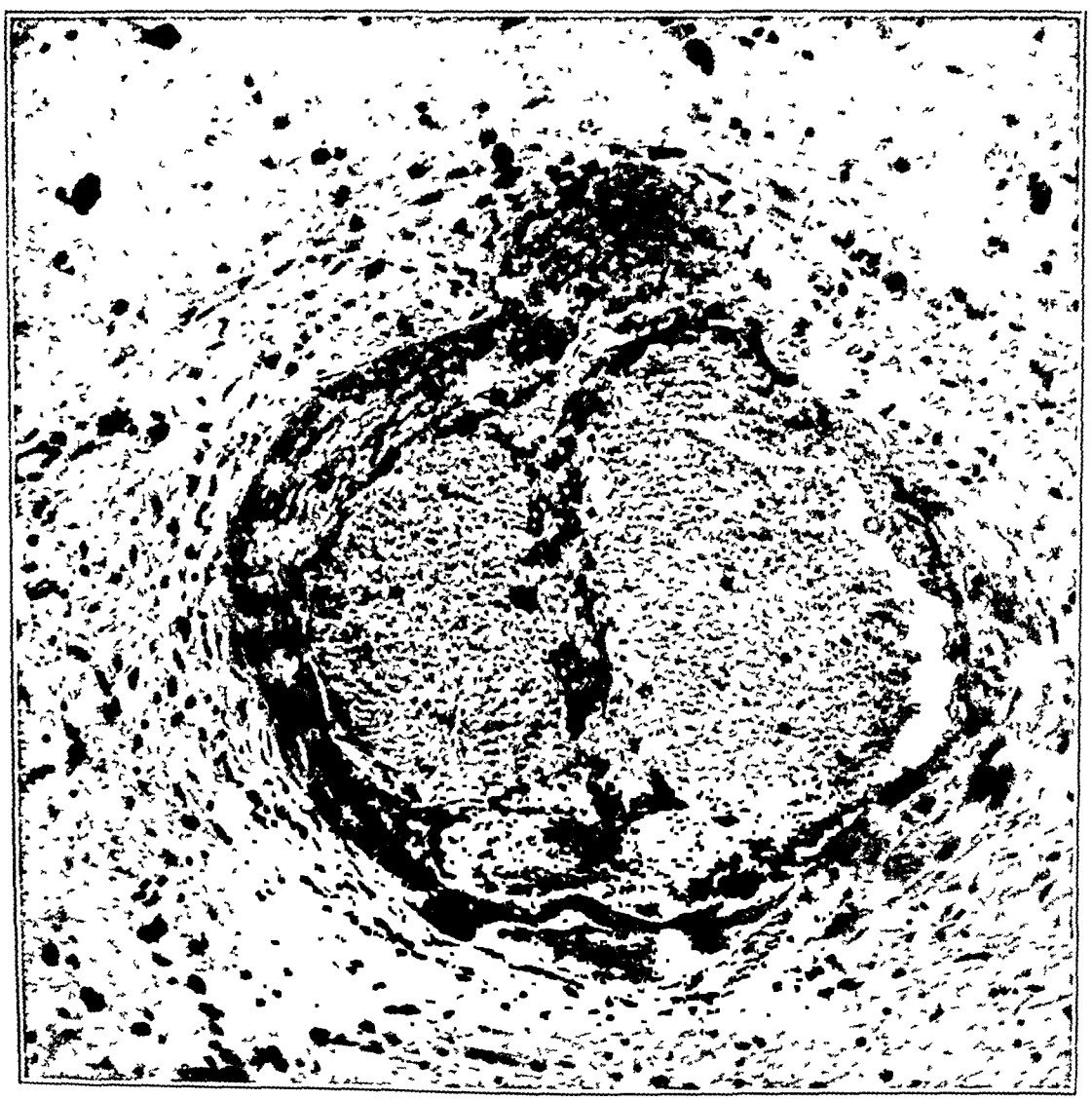


Fig. 7.—Increased permeability of a maximally distended vein for red blood cells and serous fluid. Note the degeneration and necrosis of the vessel wall. Hematoxylin and eosin; × 160.

Globus and Strauss,[8] after an extensive pathologic study, came to the conclusion that a prehemorrhagic stage of softening must antedate the apparently abrupt and explosive vascular insult. They expressed the belief that the area of softening which existed before the hemorrhage for various lengths of time was probably caused by closure of a blood vessel in the course of a vascular disease of the brain.

### SUMMARY OF THE PATHOLOGIC CHANGES

In the literature stress is laid on the arterial origin of cerebral hemorrhage. The present study has indicated that reversible, as well as permanent, structural alterations of veins may play a major role in the development of massive cerebral hemorrhage. From a microscopic study of a large number of ball hemorrhages the following points concerning their pathogenesis emerged:

Within a large majority of these hemorrhages there were one or several tremendously distended and congested veins, the walls of which displayed

6. Schwartz, P.: Die Arten der Schlaganfalle des Gehirns und ihre Entstehung, Berlin, Julius Springer, 1930.

7. Ricker, G.: Die Entstehung der pathologisch-anatomischen Befunde nach Hirnerschutterung in Abhangigkeit vom Gefässnervensystem des Hirnes, Virchows Arch. f. path. Anat. **226**:180, 1919.

8. Globus, J. H., and Strauss, I.: Massive Cerebral Hemorrhage, Arch. Neurol. & Psychiat. **18**:215 (Aug.) 1927.

advanced disintegration, with increased permeability for serous fluid and red blood cells. In only relatively few instances, and when the hemorrhagic lesion was more extensive, was it difficult or impossible to be sure of the source of the hemorrhage, mainly because of advanced disintegration of tissue and abundance of blood. In these lesions the veins were represented by a mere shadow of the wall, which had undergone almost complete degeneration, and the venous content was continuous with the extravasated blood.

In the extrahemorrhagic nerve tissue the changes consisted of compression and edema with but few exceptions. The majority of the hemorrhages were found to be outlined by a ring of edematous tissue. A zone of frank encephalomalacia could be detected in the vicinity of only some hemorrhagic lesions. Miliary aneurysms, of the type described by Charcot and Bouchard, were not found in the lesions examined.

The alterations of the veins were not confined to the areas of hemorrhage; in fact, these changes were found in areas far remote from the hemorrhagic lesions.

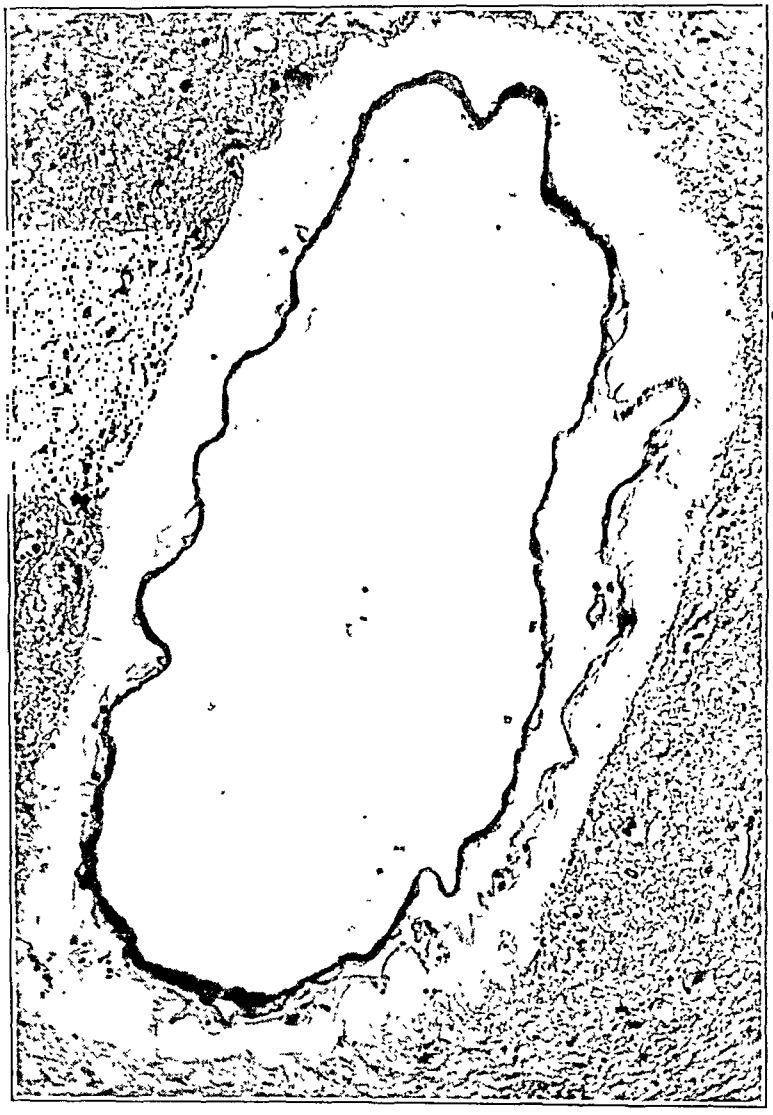


Fig. 8.—Cross section of a large vein from the basal ganglia displaying an extreme degree of atrophy. Hematoxylin and eosin; × 125.

## PATHOPHYSIOLOGY OF CEREBRAL HEMORRHAGE

A theory of the mechanism responsible for cerebral massive hemorrhage has been developed. In cases of arterial hypertension it is a terminal phase in a chain of events which has its beginning in reversible vascular disturbances of prolonged duration and repeated occurrence. These repeated vasoparalytic phenomena lead to stasis and congestion of veins and capillaries; it may be assumed that these vascular phenomena are at first transient and reversible. The effect of the repeated alterations in circulation, with

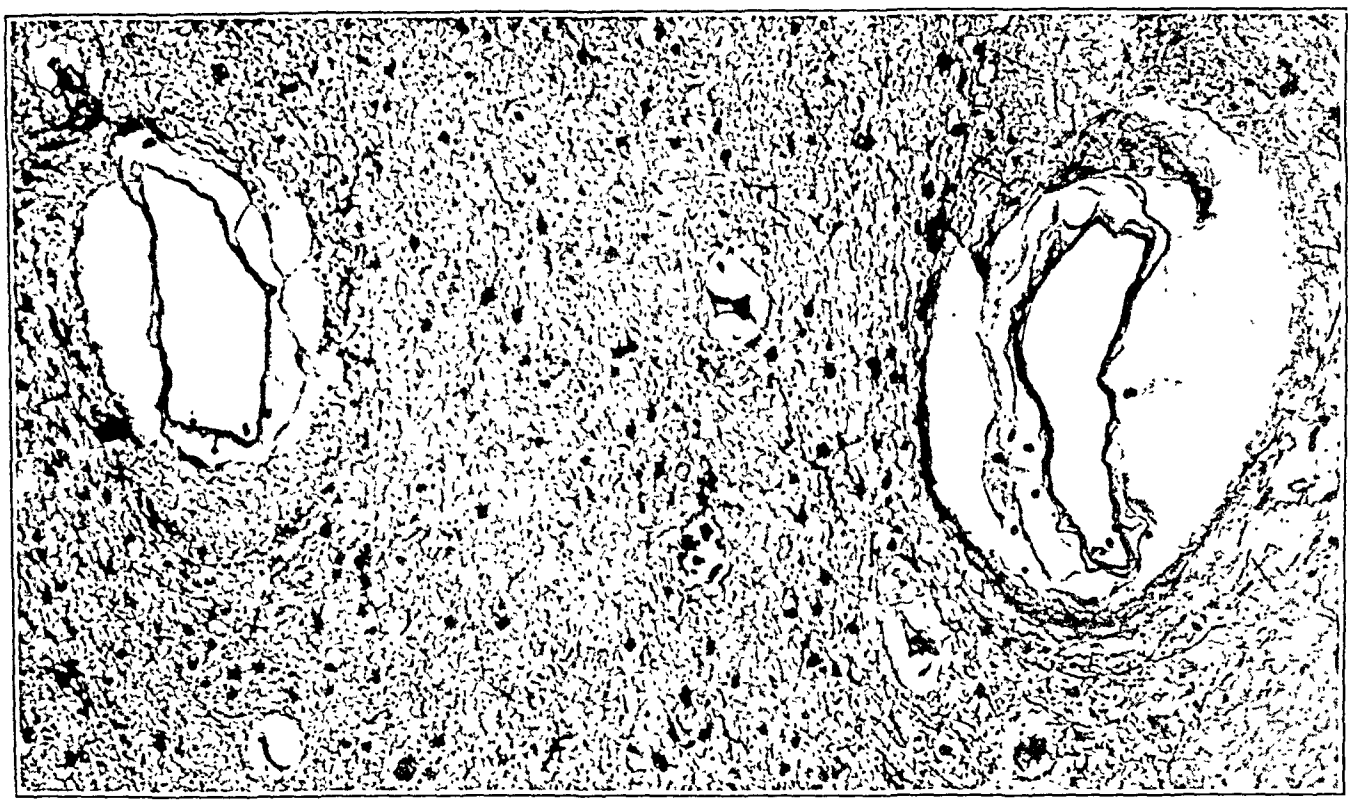


Fig. 9.—Atrophic changes of smaller veins. Hematoxylin and eosin; × 160.

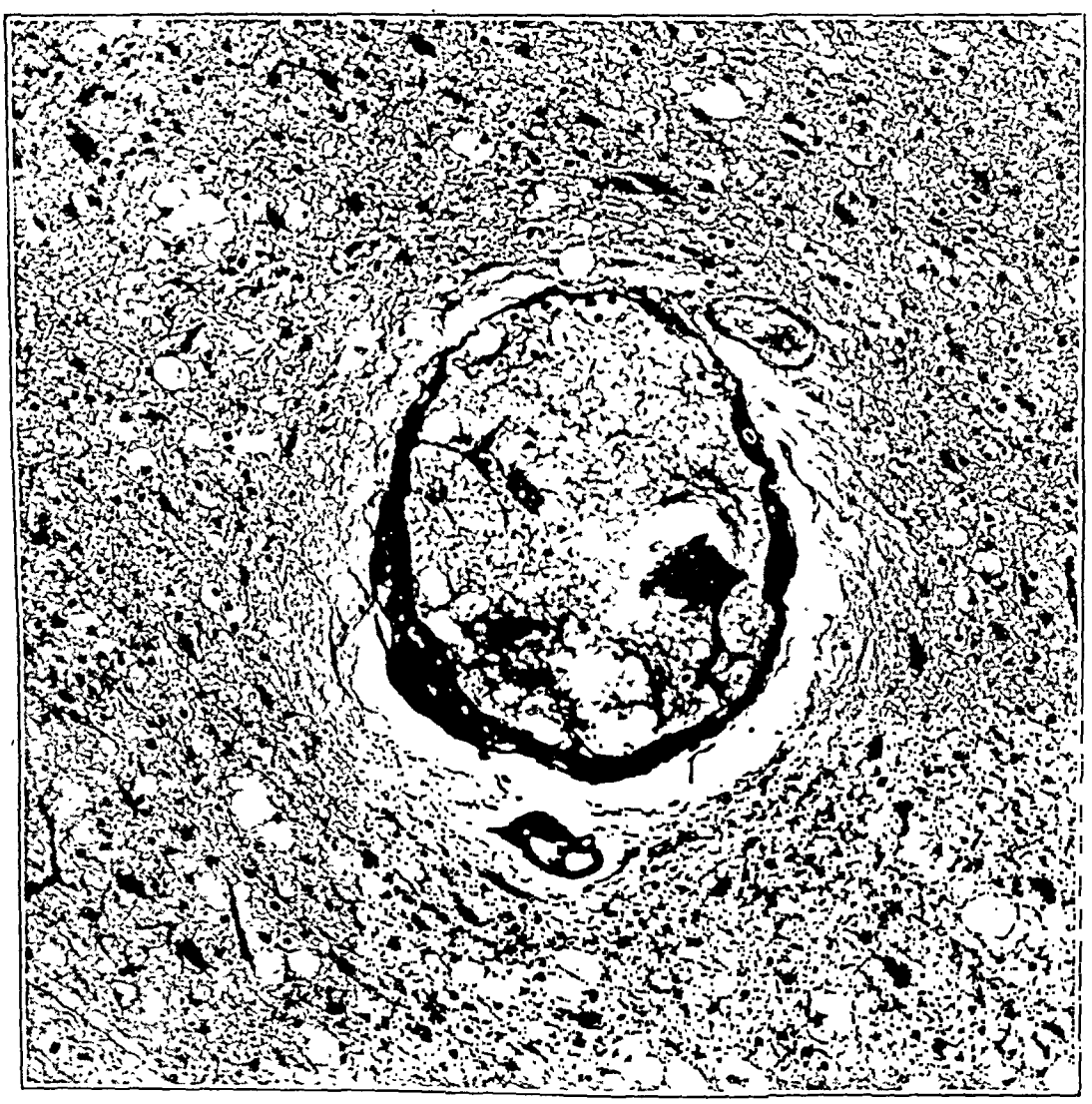


Fig. 10.—Far advanced degeneration of a maximally distended vein. The entire wall is transformed into a structureless, homogeneously stained, necrotic ring. Hematoxylin and eosin; × 160.

prolonged periods of stasis and venous congestion, may finally result in structural lesions of the cerebral veins (distention and thinning and atrophy of the vascular wall). The changes, at first minimal, advance with each episode of slowing down of the local blood circulation and stasis, to which the inadequately nourished, thin-walled veins are most likely to be vulnerable. Finally, far advanced degeneration and necrosis of their walls occur (figs. 10, 11 and 12).

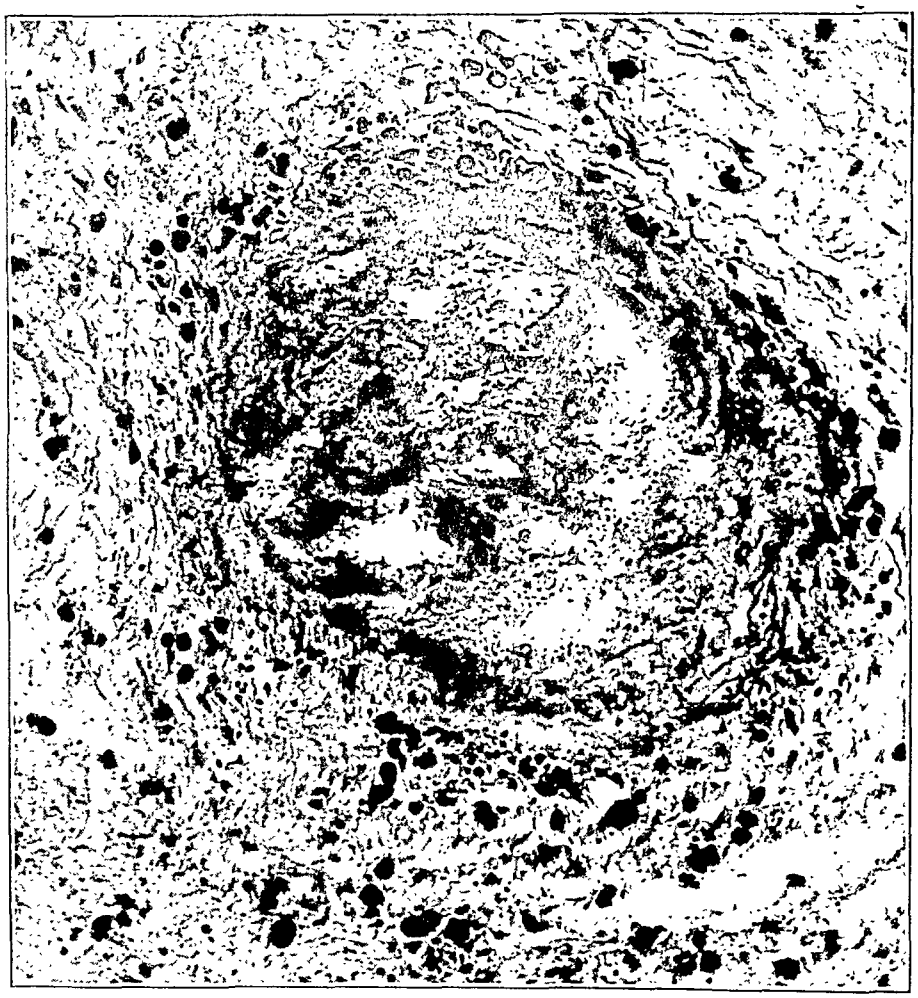


Fig. 11.—A larger vein with a completely misshapen and disintegrated wall, surrounded by a large accumulation of blood pigment and edematous nerve tissue. Hematoxylin and eosin; ×160.

These veins are no longer able to withstand elevations of venous pressure and may give way at some points in their course, thus resulting in cerebral hemorrhage. The size of the resulting hemorrhage depends largely on the size of the altered vein. In areas in which only a small vein is involved the end result is the ball hemorrhage. If a large vein is involved, a gross hemorrhage results.

Data in support of this theory are furnished by the following observation.

## OCCURRENCE OF MASSIVE CEREBRAL HEMORRHAGE ASSOCIATED WITH OBSTRUCTION OF CEREBRAL VEINS

In view of the assertions made by some authors that massive bleeding must be arterial in origin, it seems appropriate to marshal additional evidence for the venous origin of cerebral hemorrhage.

A white woman aged 27 was admitted to the hospital because of repeated left-sided convulsions. Four weeks before her admission edema had developed, which progressed from the right wrist and finally involved the entire right upper extremity, the breast and the right side of the face. During her stay in the hospital flaccid paralysis of the left extremities developed. The patient died on the seventh day in the hospital, with signs of pulmonary edema.

Gross examination of the brain revealed striking fulness of the veins over the right cerebral hemisphere, some of which measured 2.5 cm. in width. There were marked dilatation and tortuosity of the smaller veins. The right hemisphere was considerably larger than the left. Coronal sections of the brain revealed an extensive

massive hemorrhage, involving chiefly the white matter of the right frontal, parietal and occipital lobes (fig. 13).

Microscopic examination disclosed thrombosis of some of the larger pial veins (fig. 14) and a tremendous degree of passive congestion and stasis of all veins of the right hemisphere. Whereas the cortical ribbon disclosed typical softening, the lesions in the white matter were characterized by a large number of coalescent perivenous hemorrhages.

The occurrence of extensive hemorrhagic lesions in association with venous stasis was convincingly demonstrated by Cobb and Hubbard.[9] cerebral injury[11] and infectious processes[12] ("meningoleucoencephalitis"). The effects of thrombosis of the smaller veins have been recently described under the heading of "vasothrombosis."[13]

The selective involvement of the white matter in cases of fat embolism,[14] arsphenamine encephalopathy,[15] carbon monoxide intoxication,[16] late post-traumatic changes[17] ("atrophic sclerosis of the white matter"), cerebral swelling and edema[18] and diffuse sclerosis of the white mat-

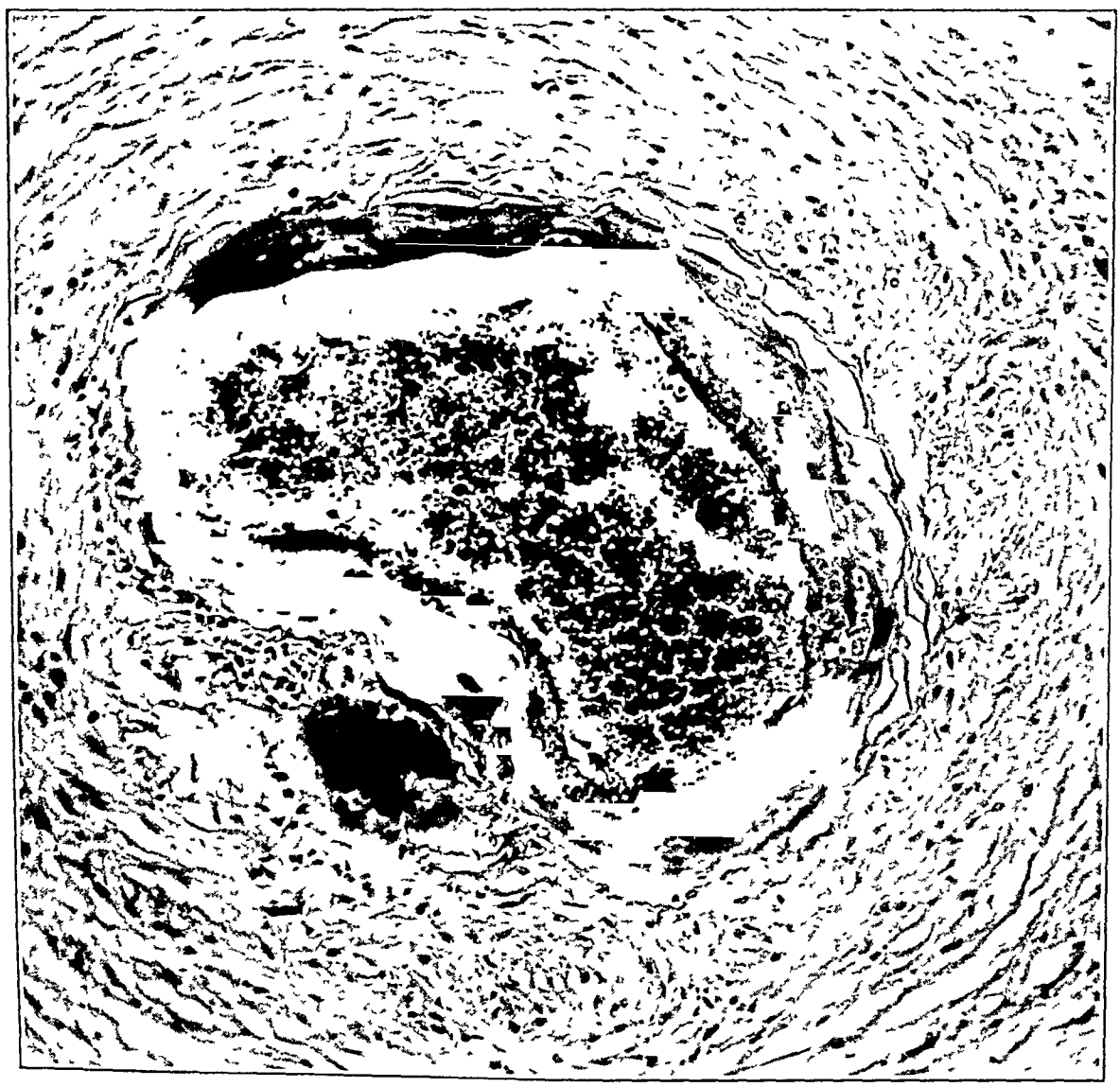


Fig. 12.—Adventitia of a vein distended with extravasated blood, merging with a small hemorrhage of the surrounding nerve parenchyma. Hematoxylin and eosin; × 160.

## GENERAL PRINCIPLES OF VENOUS DRAINAGE OF THE BRAIN

Knowledge of the venous system is required for an understanding of the predominant localization and distribution of cerebral hemorrhage. The importance of the venous circulation has been emphasized in cases of multiple sclerosis,[10]

9. Cobb, S., and Hubbard, J. P.: Cerebral Hemorrhage from Venous and Capillary Stasis: Report of Five Cases with Autopsy, Am. J. M. Sc. **178**:693, 1929.

10. Putnam, T. J.: The Pathogenesis of Multiple Sclerosis: A Possible Vascular Factor, New England J. Med. **209**:786, 1933; Studies in Multiple Sclerosis: IV. "Encephalitis" and Sclerotic Plaques Produced by Venular Obstruction, Arch. Neurol. & Psychiat. **33**: 929 (May) 1935; Evidences of Vascular Occlusion in Multiple Sclerosis and "Encephalomyelitis," ibid. **37**: 1298 (June) 1937. Scheinker, I. M.: Histogenesis of the Early Lesions of Multiple Sclerosis: I. Significance of Vascular Changes, ibid. **49**:178 (Feb.) 1943.

*(Footnotes continued on next page)*

ter [16] has been largely explained by the character of the vascularity of the white matter.

Whereas the cortical gray matter is supplied by a tremendously dense network of capillaries, the blood supply of the white matter is composed chiefly of vascular channels of considerable length, the anastomoses of which are scanty as compared with those of the cortex. The great majority of the large vessels of the white matter are veins. In serial sections, Alexander and Putnam [19] were able to demonstrate that the large veins of the white matter drain into the venae striae terminalis and thence into the vena magna of Galen.

It is obvious that the effects of retarded circulation occurring with "vasoparalysis" or "vasothrombosis" are more apt to be observed in the poorly vascularized white matter than in the gray substance, which is richly supplied by an arborized vascular network.

Duret [20] described the long veins of the white matter as *veines medullaires,* but he did not note their topographic arrangement. Pfeifer,[21] who described these veins as *Markvenen,* made the general statement that a certain amount of the venous blood of the white matter was not drained by the surface veins but flowed toward the ventricles.

Schlesinger,[22] in his interesting experimental study on venous drainage of the brain, referred to the large venous channels of the white matter as "intracerebral anastomotic veins." They

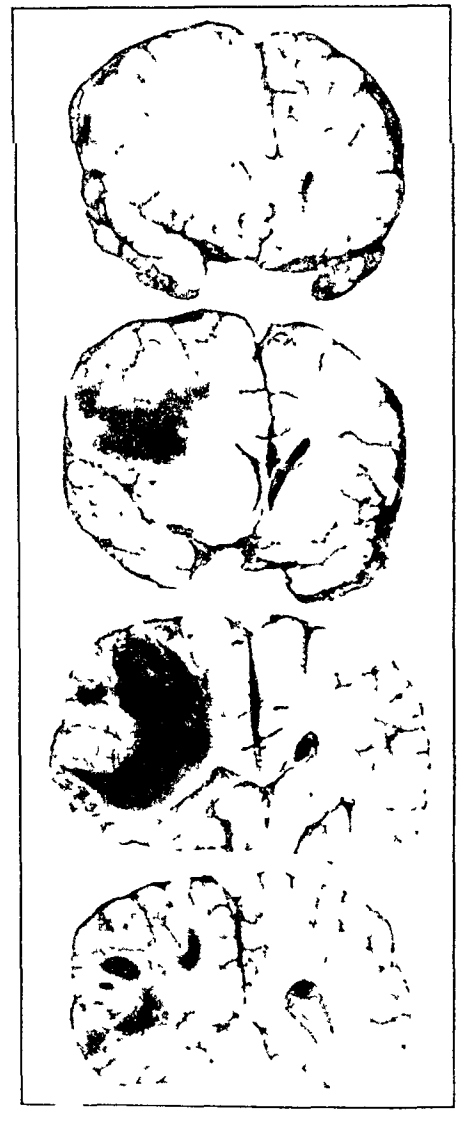


Fig. 13.—Extensive massive hemorrhage involving chiefly the white matter of the right hemisphere.

arise in the region of the angle of the lateral ventricle and establish the main intracerebral connections between the great vein of Galen and the veins of the surface of the brain. The cali-

11. Scheinker, I. M.: Vasoparalysis of the Central Nervous System: A Characteristic Vascular Syndrome, Arch. Neurol. & Psychiat. **52**:43 (July) 1944.

12. Scheinker, I. M.: Leucoencephalitis Associated with Purulent Leptomeningitis (Meningoleucoencephalitis), J. Neuropath. & Exper. Neurol. **4**:164 (April) 1945.

13. Scheinker, I. M.: Vasothrombosis of the Central Nervous System: A Characteristic Vascular Syndrome Caused by a Prolonged State of Vasoparalysis, Arch. Neurol. & Psychiat. **53**:171 (March) 1945.

14. Scheinker, I. M.: Formation of Demyelinated Plaques Associated with Cerebral Fat Embolism in Man, Arch. Neurol. & Psychiat. **49**:754 (May) 1943.

15. Scheinker, I. M.: Genesis of Encephalopathy Due to Arsphenamine, Arch. Path. **37**:91 (Feb.) 1944.

16. Scheinker, I. M.: Lesions of the White Matter of the Central Nervous System, to be published.

17. Evans, J. P., and Scheinker, I. M.: Histologic Studies of the Brain Following Head Trauma: IV. Late Changes; Atrophic Sclerosis of the White Matter, J. Neurosurg. **1**:306, 1944.

18. Scheinker, I. M.: Cerebral Swelling and Edema Associated with Cerebral Tumor, Arch. Neurol. & Psychiat. **45**:117 (Jan.) 1941.

19. Alexander, L., and Putnam, T. J.: Pathological Alterations of Cerebral Vascular Patterns, A. Research Nerv. & Ment. Dis., Proc. **18**:471, 1938.

20. Duret, H. M.: Recherches anatomiques sur la circulation de l'encéphale, Arch. de physiol. norm. et path. **6**:60, 316 and 664, 1874.

21. Peifer, R.: Die Angioarchitectonik der Grosshirnrinde, Berlin, Julius Springer, 1928.

22. Schlesinger, B.: The Venous Drainage of the Brain with Special Reference to the Galenic System, Brain **62**:274, 1939.

ber of these large veins does not appreciably change during their course. According to Schlesinger, the large anastomotic veins do not break up into capillaries but are joined only at relatively long intervals, and in most instances at right angles, by short venules. A second group of large veins can be seen in the basal ganglia, which he called longitudinal lenticular veins. Some of them perforate the internal capsule and reach the lateral surface of the putamen, traversing the outer layers in this structure. Their distribution is shown in figure 15. The large lenticular veins leave the substance of the putamen, enter the external capsule and open into the deep sylvian veins. Schlesinger noted that injected veins in the basal ganglia in man grossly resemble those in the monkey.

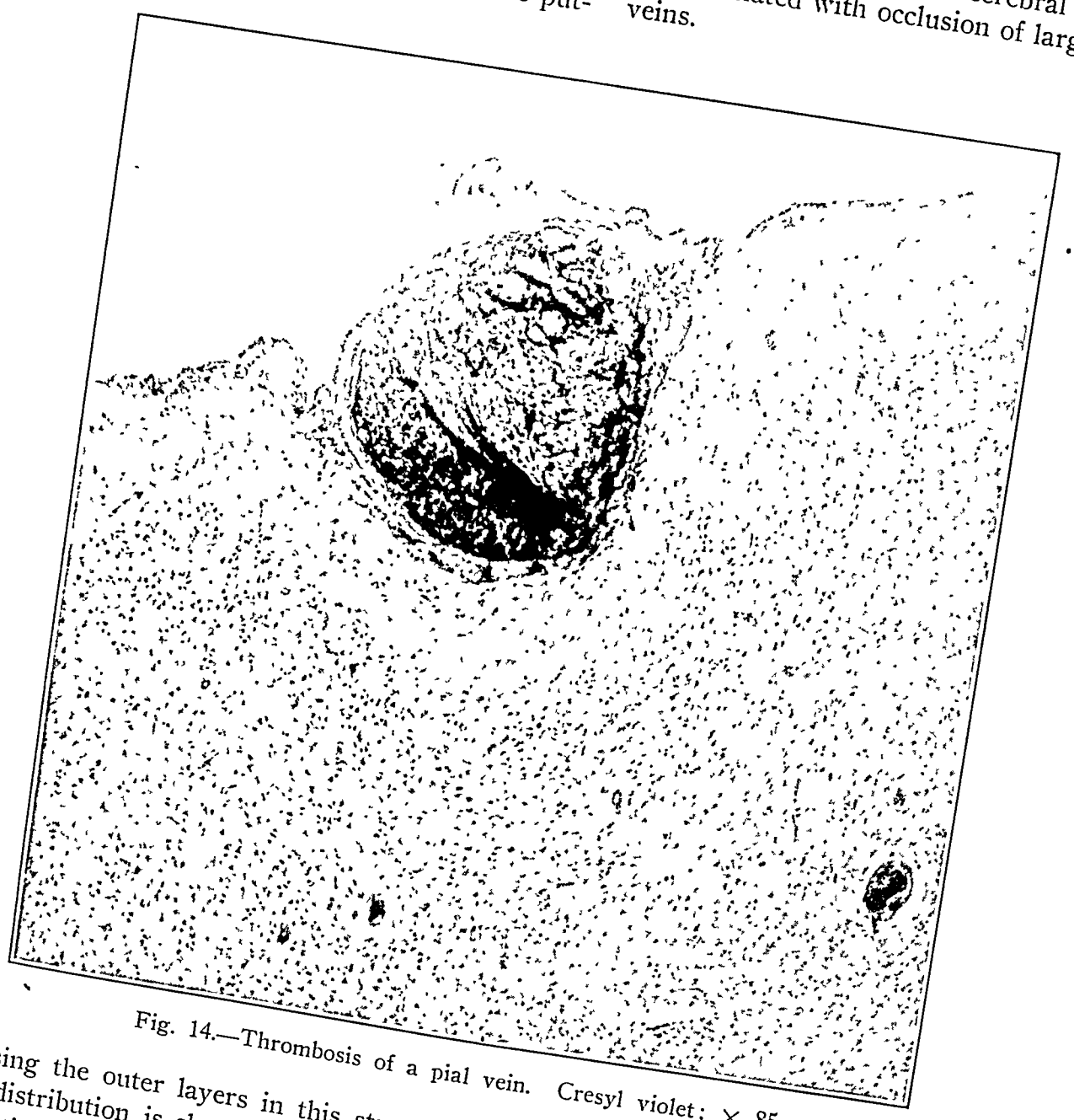


Fig. 14.—Thrombosis of a pial vein. Cresyl violet; × 85.

## PREDOMINANT LOCALIZATION OF MASSIVE HEMORRHAGES

In theory any cerebral blood vessel may be the source of hemorrhage. It is generally known that areas involved by hemorrhages, although varying in exact location in individual cases, are most frequently encountered in the general neighborhood affecting the thalamostriatal region. Next in frequency are the hemorrhages in the cerebral white matter and in the brain stem. The latter are most frequently secondary to transtentorial herniation of the brain stem.[2] The hemorrhages of the cerebral white matter are associated with occlusion of larger superficial veins.

Many theories have been offered to explain the frequent occurrence of hemorrhages in the thalamostriatal region. The following explanation emerges from the present study: The size of the hemorrhagic lesion depends largely on the size of the altered blood vessel. It has been demonstrated that the largest veins are found within the basal ganglia (longitudinal lenticular veins) and in the central white matter (intracerebral anastomotic veins). This localization of the large veins may explain at least in part the predominant occurrence of massive

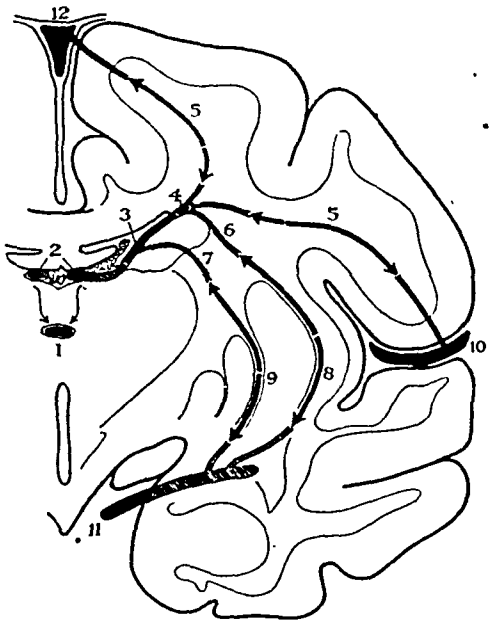



Fig. 15.—Diagrammatic distribution of large lenticular veins perforating the internal capsule and the basal ganglia in the brain of the rhesus monkey. *1* is the great vein of Galen; *2*, small veins of Galen; *3*, transverse caudate vein; *4*, longitudinal caudate vein; *5*, venous channels, connecting the great vein of Galen with the superior longitudinal sinus and the superficial sylvian vein; *6* and *7*, superior external and internal lenticular veins; *8* and *9*, inferior external and internal lenticular veins; *10*, superficial sylvian vein; *11*, deep sylvian vein, and *12*, superior sagittal sinus. From Schlesinger.[22]

hemorrhages within the basal ganglia and the white matter.

## SUMMARY

The venous alterations associated with hypertensive disease of the brain have been studied in 65 cases, in most of which there were two types of lesions: (*a*) reversible changes, manifested by venous congestion and stasis, resulting in tremendous distention, and (*b*) structural alterations of the vessel wall, characterized by an extreme degree of atrophy and advanced signs of degeneration and necrosis.

Attention is directed to the predominantly venous origin of cerebral hemorrhage, which is considered as a terminal phase in a sequence of events which have their beginning in reversible vascular disturbances. In a later stage structural alteration of the cerebral veins occurs, and terminally degeneration and necrosis of the vessel wall are present.

*In the presence of far advanced venular* atrophy elevation of venous pressure would appear to be an essential precursor to the massive escape of blood.

Cincinnati General Hospital.

# PSYCHOLOGIC STUDIES ON A PATIENT WHO RECEIVED TWO HUNDRED AND FORTY-EIGHT SHOCK TREATMENTS

JOSEPH PERLSON, M.D.
Chief of Neuropsychiatry San Bernardino County Hospital
SAN BERNARDINO, CALIF.

Since Sakel's discovery of insulin shock herapy, in 1933, and the introduction of electric hock by Cerletti and Bini, in 1938, the most requent questions asked are: What is the ultiate effect of repeated induced convulsive eizures? Are organic changes produced?

The investigators who have reported histoogic changes in the brain have not been in substantial agreement with each other. Whereas he problem 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. The opponents and proponents of shock therapy have sparred back and forth from enthusiasm to conservatism, and even condemnation. There are those even who have posed the possibility that electrically induced seizures lead to epilepsy in a person so predisposed. Nevertheless, there is sufficient evidence that cerebral function is disturbed. Not only are electroencephalographic changes present during the treatment, but the mental changes give evidence of organic changes. Still, most effects on the whole are reversible, and even the most dramatic mental symptoms of organic origin usually disappear eventually.

In view of this disagreement, it is necessary to follow the patients who have received this form of therapy and to observe the results not only immediately, but months and years, after the treatment. It must be ascertained whether their intellectual performance is on a level with their best normal activity.

The following case is presented because I can find no report in the literature in which a patient received so many induced convulsions without any discernible intellectual or physical sequelae.

## REPORT OF A CASE

A white man, aged 27, was first admitted to the Patton State Hospital as a voluntary patient on March 15, 1942. The anamnesis obtained from a brother was essentially as follows: The first symptoms of mental illness became known in April 1937, on receipt of a cablegram from the American Consul in Shanghai. Prior to this, the patient had left in August 1936 to attend school in Germany, but, because of the gathering war clouds, he left a short while later for China. He called on the Consul for help because he felt he was being followed and voices were calling him from the street lamps. Soon after, he jumped from the second story of a boarding house in an attempt to run away from imaginary followers and received fractures of the right arm, the patella and the ankle. Previously he had locked himself in his room and would not eat.

His relatives made the trip to China and brought him back. Because he was disturbed, he required mechanical restraint much of the way. On his return he was taken to a sanatorium but was removed in October 1937. After this, he became suspicious of strangers and took jaunts into the hills with his dog, staying away from two to five days at a time, regardless of weather conditions. He joined the Y. M. C. A. to make himself physically fit and got a job in an airplane factory, from which he was soon discharged.

He then left home and worked on a grape ranch. When the season was over, he returned and went to the California Institute of Technology to do postgraduate work. There he received credit for completion of one-half the work required for the degree of Master of Arts. In February 1941 he enlisted to become a flyer at an aviation school and graduated in September 1941. He was then stationed at McClellan Field, in Sacramento, as an Army transport pilot. From there he went east on maneuvers but was grounded in December because of an argument with an officer. Several weeks later he was sent to the Letterman General Hospital.

When seen in January 1942, he was delusional and suspicious of both officers and physicians. In February he was removed from the hospital and brought to southern California. After this, he would not converse and would not drink water or eat solid food, although he drank large quantities of milk and ate some bread. He claimed he was cold and kept the house at 75 F. while sitting on the floor radiator. He would not engage in any activities, because he asserted he was wired and it would disturb other people. He wanted his ear drums punctured so that he would be deaf and thereby his troubles would disappear. He had placed salve in his ears and stuffed them with paper. He believed that he was changing from man

From the Patton State Hospital, Patton, Calif.

to woman, that his breasts were enlarging and that he was losing his beard.

On the day of admission to the Patton State Hospital, he was resistive and assaultive and stated that he could not stand confinement. The next day he demanded his release, fought and kicked and attempted to break out of the door. He then became catatonic, refusing to talk or eat and required tube feeding. Two days later he was discharged and legally committed.

Because of his disturbed condition, a mental examination was not made. The working diagnosis was dementia praecox, paranoid type with catatonic features. The general physical and neurologic examinations revealed an essentially normal status. The blood pressure was 128 systolic and 80 diastolic. The results of routine laboratory examinations, including the Wassermann test of the blood and urinalysis, were also normal.

The patient was in and out of restraint for a total of one hundred and fifty-three days, from March 16, 1942 to May 22, 1944. The following reasons were given: He was combative, assaultive, destructive and delusional. He imagined that people were talking about him, framing him and calling him a sexual pervert and other names; that his brothers were in the ward and demanding that they be brought to him; that people were putting a radio beam on him and trying to destroy his mind; that government officials were waiting for him in the office; that the hospital was being bombed by planes. He was dangerous to himself in that he butted his head against the walls and pounded the doors and the back of his neck with his fists.

In order to control his violence (sedation failing), it was necessary to give him almost daily shock treatments. Thus, up to Nov. 2, 1942 a total of 94 convulsions were induced with metrazol, the maximum dose necessary being 13.5 cc. Up to Dec. 16, 1944, he received 152 electric shocks, with an average current of 700 milliamperes for three-tenths second. In addition, he received two treatments of electric narcosis, the last being on Nov. 19, 1942; one was for thirty seconds, at 200 milliamperes and the other for ninety seconds, at 70 milliamperes. The machine used was one of a type constructed by the California Institute of Technology. The first evidence of sustained recovery appeared in September 1944 and was maintained until his parole from the hospital.

A general physical examination on Dec. 26, 1944 showed that his condition was completely normal; the blood pressure was 124 systolic and 76 diastolic. The results of neurologic examination and examination of the eyegrounds were entirely normal. A spinal puncture on Dec. 28, 1944 revealed clear fluid and a pressure of 200 mm. of water; the Wassermann reaction was negative; the reaction for globulin was negative, and there were 5 cells per cubic millimeter. Roentgenograms of the entire spine taken the next day revealed nothing abnormal.

Beginning on December 19, extensive psychologic studies were made. In preface, it should be stated that at the age of 12 years and 10 months the patient attained an intelligence quotient of 130 on the Stanford Achievement Test; at the age of 14 years and 6 months he had an intelligence quotient of 116 on a general intelligence test.

At this time six tests were made. First, the Otis Employment Test 1, which is a simple verbal test of mental ability, was given. On this test he made a total score of 70, which is the equivalent of the score made by 71 per cent of the general population. Next, the American Council on Education Psychological Examination, 1940 College Edition, was given. This test correlates satisfactorily with progress in college work. On this test he scored a total of 106, with a percentile score of 65. This score is considered to be a satisfactory indication of normal progress in college study. Then the Ohio State University Psychological Examination, Form 21, was given. Here he made a total score of 105 and a percentile rank of 77. This result was definitely higher than that on the previous test, indicating that the absence of a time limit in the Ohio State test was a determining factor. Next, the Bennett Test of Mechanical Comprehension, Form AA, was given. On this test he made a percentile score of 95 as compared with a group of engineering school freshmen, a result which would indicate a high order of ability in perceiving mechanical relationships. Next, he was given the Likert and Quasha Revised Minnesota Paper Form Board Test, Series AA. This is a timed test of spatial perception. Here he made a percentile score of 20 as compared with engineering college seniors, or a percentile score of 55 as compared with students in liberal arts college. The difference in accomplishment between this test and the preceding one is traceable to the necessity of working under the pressure of time. Finally, the Kuder Preference Record Test, Form BB, was given. This test is used in school and college counseling as a preliminary appraisal of fields of vocational interest. Here he showed a heavy weight of interest in scientific and mechanical activities, with a rather low weighting in persuasive, musical and clerical activities.

From the results of these tests, it was concluded that the patient was intellectually capable of a slightly better than average level of college scholarship, and, further, that he was of superior ability as compared with the total population and had undergone no greater change in intellectual capacity than is normal with increasing age. Qualitatively, he showed only an inability to do well in a speed test. With regard to the latter, however, it might be mentioned that relatives of the patient claim that now he is more alert and quicker than ever before.

The mental examination in January 1945 disclosed nothing of importance in the family history. His birth and early development were normal. In the sexual sphere, he admitted the practice of fellatio at the age of 10 for a period of one year and of intercourse in ano at 20 years of age. He masturbated as often as three times daily. However, he had had normal heterosexual experiences. He claimed that he had never married because of the lack of opportunity and his poor financial condition. He denied alcoholic indulgence. As regards social adaptability, he stated that

he was friendly but self conscious. He enjoyed the company of both sexes, but he was mostly in association with boys and enjoyed male parties. He stated that he was afraid to be too friendly with persons below his social standards. His other adjustments appeared to be within normal limits, and his medical and surgical history was essentially without significance. No gross intellectual or emotional impairment was elicited.

The conclusion based on an electroencephalographic examination, made on Feb. 1, 1945, was borderline cerebral dysrhythmia without localization.

On Feb. 7, 1945 the patient was paroled, and it is understood that he is now making a satisfactory social and occupational adjustment.

## CONCLUSION

The benefits derived from convulsion therapy usually far outweigh the possible complications which may occur. It appears from this case that convulsive shock therapy does not lead to intellectual, emotional or physical deterioration.

Dr. Clemson Marsh, White Memorial Hospital, Los Angeles, made the electroencephalographic study, and Mr. J. W. McDaniel, psychologist, of the San Bernardino Valley Junior College, made the psychologic tests.

3239 H Street.

# News and Comment

## POSTGRADUATE COURSE IN PSYCHIATRY, McGILL UNIVERSITY

McGill University has announced a four year postgraduate course in psychiatry, leading to a diploma. The prerequisites for this course are a degree from an approved medical school or college, a general internship of one year's duration and satisfactory personal qualifications.

The course is designed to prepare men primarily for work in teaching, research, community psychiatry and consultation. It includes experience in the Allan Memorial Institute of Psychiatry and in the wards and the outpatient departments of the Royal Victoria Hospital. Part of the time is spent in dealing with long term cases in designated mental hospitals, in neurology and neuropathology and in community psychiatry.

## MEDICAL CORPS, NINTH SERVICE COMMAND

A conference on neuropsychiatry by members of the Medical Corps of the Ninth Service Command was held at the Bushnell General Hospital, Brigham City, Utah, on Oct. 1 and 2, 1945.

Col. Lauren H. Smith, consultant in neuropsychiatry of the Ninth Service Command, was in the chair.

The meeting was opened by Brig. Gen. Robert M. Hardaway and Brig. Gen. William C. Menninger. The following papers were presented: General Therapeutic Program in an Army General Hospital, Col. Olin B. Chamberlain; Convulsive Shock Therapy in an Army General Hospital, Lieut. Col. Mark Zeifert; Subconvulsive Insulin Shock Therapy, Major Daniel J. Sullivan; Psychotherapy of the Neurologically Disabled Soldier, Lieut. Col. Edward O. Harper and Capt. Edward C. Clark; Emotional Adjustment of Newly Blinded Soldiers, Lieut. Col. H. D. Shapiro; Reeducation of Aphasic Patients, Lieut. Joseph M. Wepman; Treatment of Psychiatric Patients in an Army Regional Hospital, Major Arthur M. Kasey Jr. and Capt. C. E. Stanfield.

## NEUROPSYCHIATRIC INSTITUTE OF CLEVELAND

The Neuropsychiatric Institute of Cleveland has been established at 10528 Park Lane, Cleveland 6. Its aim is to provide clinical facilities for diagnosis and treatment of patients, as well as a research and teaching program. Seminars in neuropsychiatry have been established for physicians of the Veterans Administration in this region and for local practicing doctors.

The staff of the Neuropsychiatric Institute at present consists of Dr. J. L. Fetterman, director; Dr. M. D. Friedman, associate director; Dr. A. A. Weil, research psychiatrist, and Dr. Evelyn Katz, clinical psychologist.

## UNIVERSITY OF CALIFORNIA COURSE IN PSYCHIATRY

The University of California extension division, in cooperation with the Division of Psychiatry, University of California Medical School, announces a twelve weeks' refresher course in psychiatry for physicians returning from military service, starting Jan. 7, 1946, at the Langley Porter Clinic, San Francisco Campus, University of California Medical School.

Instruction will be given under the direction of Dr. Karl M. Bowman, professor of psychiatry, of the division of psychiatry of the University of California Medical School, with the assistance of staff members from other divisions of the medical school. Subjects to be covered will include general psychiatry, functional and organic psychoses, psychoneuroses, therapy, psychosomatic problems, neuroanatomy, clinical neurology, neuropathology, roentgenographic diagnosis and other related topics.

Registration is open to graduates of approved medical schools with nine months' general internship. Preference will be given to applicants with training in psychiatry, to those preparing for examination by the American Board of Psychiatry and Neurology, to graduates of the University of California Medical School and to legal residents of the state of California.

The fee for the course will be $200, payable in advance.

Immediate application for registration is recommended, because of the limited enrolment which can be accommodated. Application should be made by letter containing the following information: (1) place of legal residence; (2) medical school attended and date of graduation; (3) experience and training, with special details regarding psychiatric training, and (4) record of military service. Address applications to: University Extension, University of California, 540 Powell Street, San Francisco 2. Check or money order to cover enrolment fee and made payable to the Regents of the University of California should also be enclosed, unless registration is under G. I. Bill of Rights, in which case only application is necessary. Further details regarding the course may be obtained from the above address.

# Obituaries

## PÍO DEL RÍO-HORTEGA, M.D.
## 1882-1945

Pío del Río-Hortega [1] was born in the Spanish own of Valladolid, in the district of Old Castile, n May 5, 1882. His father, del Río, inherited a astle in the nearby countryside, but it had long go fallen into ruin; and so the boy went to school n the city and his family occupied a house there which formed one whole side of the principal laza.

His boyhood was apparently a happy one, and e enjoyed its recollection. He often recalled the ull baitings which were staged in the plaza once ach year, while townspeople, dressed in their est, watched from balconies. He liked to tell how the young bull was played but never harmed and how an energetic beast once charged out of the square and up a stairway that led into his own house. He was wont to contrast this harmless sport with the brutality of the professional bull fight, which he disliked and would never witness.

He entered the University of Valladolid and graduated in medicine, after which he began to practice; but this did not satisfy his keen, restless mind. He returned to the histologic laboratory and later obtained a traveling fellowship, which took him to Paris and also for a few weeks to London. Then he returned to Spain and journeyed up to Madrid, anxious to work with Spain's most brilliant scientist, Don Santiago Ramón y Cajal, who was then at the height of his renown. Cajal was a national figure of much importance because of the recognition that had come to him from abroad for his scientific work and because of his ability as a writer, artist and leader of thought; a rugged sort of man of peasant stock, a man looked on by his countrymen as the prophet of a new order.

Hortega was a Spaniard of a different type—shy, sensitive, aristocratic, proud, and yet he resembled the master in that he was an artist and an eager perfectionist. He was accepted, and Cajal set him to work for a time with Achúcarro and later took them both into his own, third story laboratory with his other disciples, Tello, Lafora, de Castro and others.

At the time of Hortega's arrival, Cajal had turned from his work on neurons and neuron connections, which had brought him a share in the Nobel prize of 1906, to the study of neuroglia. In 1913 he had published his monumental contribution on the astrocyte.[2] The work was based on a new method of metallic impregnation (gold chloride–mercury bichloride method). But in this study Cajal had pointed out that there remained a large group of small cells in the central nervous system that did not seem to be neurons but that were, nevertheless, resistant to staining by any existing neuroglial method. To these cells Cajal had given the title of the "third element" in the central nervous system.

Hortega began his work by using the standard laboratory methods and learned microscopic drawing from the master. Outside the laboratory, he occasionally turned his attention to painting of a classic type, as shown by a full length picture of one of the saints, done in the Spanish style of "sacred art," which later hung in his home.

After a year or two he turned his attention to Cajal's third element, and, encouraged by Achúcarro, he began to experiment with various technics. Thus, in 1916 and 1917 appeared his first publications on neuroglia studied by Cajal's methods. Then, in 1918, he described a new method of his own, that of ammoniacal silver carbonate. In 1919 he showed that by this method he could stain the third element, which he divided into two groups.[3] One of these groups he named microglia and the other, which he described fully in 1921, he named oligodendroglia.[4]

It now became clear that microglial cells truly represented a third element: They were of mesodermal origin, corresponding to the reticuloendothelial cells found elsewhere in the body, cells which were readily transformed into mobile macrophages by destructive processes in the surrounding brain.[5] The oligodendroglial cells, on the other hand, were in reality smaller neu-

1. Pío decided early to use his father's and mother's names joined by a hyphen, instead of separately, as is the custom in Spain.

2. Ramón y Cajal, S.: Trab. d. lab. de invest. biol. de la Univ. de Madrid **11**:219, 1913.

3. del Río-Hortega, P.: Trab. d. lab. de invest. biol. de la Univ. de Madrid **14**:269, 1919.

4. del Río-Hortega, P.: Bol. real Soc. españ. de hist. nat., January 1921.

5. del Río-Hortega, P.: Microglia, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, p. 483.

roglial cells which seemed to serve as neuron satellites.[6]

Del Río-Hortega now worked under the pressure of a great excitement. He made elaborate black and white drawings of these cytologic discoveries, using paint in the manner of the Spanish school, as he had been taught. He fell into the habit of taking his drawing with him to the Spiedum Coffee House, where his own group of friends met in a *tertulia* each evening at 10 o'clock. Often, after the string quartet had stopped its music and the friends had drifted off to their homes, he would carry on with his drawing in the cool of the night, elaborating the day's sketch in the company only of his friend Gómez until closing time at 2 o'clock in the morning.

Gómez, or Nicolas Gómez y del Moral, was a business man more interested in things artistic and in the amenities of life than in either science or business. A good-humored gentleman, of a type rarely found outside Spain, he was filled with admiration for the brilliance of Hortega and became his champion. Thus a friendship was formed between them at this time which was to last for thirty years.

After this startling discovery was announced by the youngest member of the "school," all did not go well in the laboratory. Jealousy of the brilliant newcomer crept in. Cajal himself was curiously loathe to accept the fact that the last of the interstitial cells of the central nervous system could have yielded their cytologic secrets to a new method.

And so it came about that while the Spanish government was taking steps to build a larger and more elaborate institute, to be named for Cajal, his most brilliant pupil left his group. But nevertheless, it was Cajal who used his influence to establish Hortega in a new laboratory at the Students' Residence (which they referred to as the Residencia), on the outskirts of Madrid. This laboratory and an adjacent laboratory of physiology, of which Prof. Juan Negrin[7] was

PÍO DEL RÍO-HORTEGA, M.D.
1882-1945

6. del Río-Hortega, P.: Neuroglia, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 2, chap. 9, p. 423.

7. Negrin later became premier of the Spanish Republic and leader of the ill fated republican forces during the civil war.

irector, were supported by a committee[8] estabshed to promote progressive education and reearch and to provide traveling fellowships. tudents flocked to Hortega's laboratory: rados, Asúa, Ortiz Picón, Costero, Calandre, acristán and others, and the single room of the aboratory was filled all day long with six to welve workers.

It was about this time (1924) that the photograph reproduced here was taken. Don Pío, as his pupils respectfully called him, was a small man, dapper, alert, quick of movement, rapid of speech, highstrung, fastidious. When he stood by one of the El Greco paintings in Toledo, his thin, aquiline profile and slender fingers showed a striking resemblance to the faces and hands of the nobles of the court of Philip II.[9] There was in his laboratory a feeling of excitement about histology. Every man was his own technician and took great pride in demonstrating his handiwork. General discussion had to do with microscopic preparations, while "small talk" turned on Spanish art and architecture, ancient and modern, instead of baseball, cricket, politics or nocturnal conviviality, as in other laboratories and other lands.

At this time the application of Hortega's discoveries to pathologic problems was becoming apparent in clinical centers, as was shown during the next few years in the publications of Percival Bailey, Cushing and Cone, in the United States; Da Fano, in England; Metz and Spatz, in Germany; Rezza, in Italy, and numerous others.

Hortega shortly turned his own attention to pathology,[10] at the Madrid General Hospital and ten years later had become director of the Cancer Institute in the newly built University City of the University of Madrid. However, his own work on pathologic subjects is of less importance than his contributions to pure histology, and it is significant that he continued to spend his mornings at the Residencia, where he worked with numerous students on normal and experimental cytology.

At that time, in 1934, he seemed much the same as he had ten years before, although he was older and was now an acknowledged leader in his field. Cajal, on the other hand, had aged greatly and had become deaf and infirm. It was apparent, however, that there was no bitterness between these two great histologists; each seemed to feel pride in the other's accomplishments, although their friends were conscious of a sort of fierce rivalry. Never did Hortega refer to his master except in terms of greatest admiration. International recognition might well have come to the pupil for his brilliant contributions, as it had to the master, if dreadful civil war had not come upon Spain.

This time, that preceded the outbreak of civil war, was for Spain a time of renaissance in art, music, science and progressive education—a renaissance eventually destroyed by Fascist might. During the siege of Madrid, Hortega remained in the city. He witnessed the complete destruction of the Cancer Institute by shell fire. His books were used to build bulwarks against snipers, and the laboratory, with its histologic treasures and microscopes, gradually dissolved in the devastation of "no man's land."

But he was neither a soldier nor a politician, and he turned back to his microscope for consolation. There followed a period in Valencia with his first pupil, Miguel Prados, when he resumed his studies for a little time. Shortly, however, he was sent to Paris by the republican Government with his friend Gómez. On reaching Paris, in 1937, this "Jonathan and David" showed the effect of the war years all too plainly. Hortega was very thin, his hair graying, his movements more nervous than ever; and he seemed to have grown a little smaller. Gómez was gaunt from privation. His clothes hung on him in folds, but this man, who had been wont to wear a cloak of an evening with the air of a grandee, was still debonair and able to laugh in the face of adversity. Hortega worked then for about a year in the laboratory of the neurosurgical clinic of Prof. Clovis Vincent, at La Pitié Hospital.

After Paris, there followed a few years in Oxford. Thanks to Prof. Hugh Cairns, a laboratory was fitted up for him in the Radcliffe Infirmary that resembled his first laboratory at the Students' Residence, in Madrid. Here he had ample pathologic material for study and was associated with a kindred histopathologist, Dr. Dorothy Russell. Gómez made a gallant effort to create a congenial atmosphere in this strange land, but the tragedy of Spain weighed heavily on Hortega; he found the English language impossible to master, and he missed the Spanish way of life.

And so, when he was offered a haven in Argentina and a university laboratory, they sailed for Buenos Aires, where for a time students again gathered about his microscope. He founded a new journal—*Archivos de anatomía normal y pathológica*. But, again, political hostility interfered with the promised development of his laboratory; ill health came, and on June 1, 1945, Pío del Río-Hortega died.

8. Junta para ampliación de studios e investigaciones.
9. The portrayal of the burial of the Count of Orgaz, which covered one wall of a church in Toledo, is a remarkable record of these Castilian courtiers.
10. Arch. españ. de oncol. **1**:477, 1930; **2**:411, 1932.

In an unpublished address [11] on "Art and Artifice in the Science of Histology," Hortega has put into words his credo. It explains the excitement and pleasure that he always showed while working at his microscope. There was for him romance and art, as well as discovery, in the land beyond the lenses.

> Histology is a respectable and respected science. It serves, among many other purposes of importance, to give prestige to the rest of medicine. In all proper publications, histology is given the chief place. At the banquet of medicine it is the guest of honor, who eats little—aloof, mysterious—to whom all listen, yet whom very few understand. . . .
>
> This science, which illuminates the structure of cells and tissues, has two facets: one cold, factual, static, which reflects only the metaphysical; the other pleasing and dynamic, which brings to light the art of the subject.
>
> I have to confess that if there were only the first aspect, with its abstruse ideas, its chimeras and its pedantic pronouncements, I could not be a histologist. Further, I firmly believe that in order to be a good histologist it is necessary to have the soul of an artist and to possess the sense of true romance. . . .

11. Translated by one of Hortega's younger pupils, Dr. William Gibson, who has allowed me to make the accompanying quotations.

> For my own part I confess that I do not know what made me become a histologist, whether it was keen ambition, a fervent desire (nearly always disappointed) to see that which no one else has seen or simply an incessant yearning to see for myself the marvels of natural structure, stripped of its disguise by means of technical artifice. . . .

Finally, he added:

> . . . The emotion which is associated with a discovery, small though it may be, generously repays the investigator for his finished labor.

Pío del Río-Hortega contributed an important chapter to knowledge of the structure of the central nervous system. He threw a clear light on the form and function of the interstitial cells. He provided the fundamental cytologic descriptions which were needed in the classification of tumors of the brain and spinal cord. He simplified and clarified the study of cytogenesis and pathologic alterations within the brain. Outside the field of cytology his influence was felt first in neurosurgery, but his work has had an influence on the study of neurologic and psychiatric disease in general which will grow in importance as the years pass.

WILDER PENFIELD, M.D.

# Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

## Anatomy and Embryology

EMBRYONIC GRAFTS IN REGENERATING TISSUE: III. THE DEVELOPMENT OF DORSAL AND VENTRAL ECTODERM OF RANA PIPIENS GASTRULAE. HENRY S. EMERSON, J. Exper. Zool. **97**:1 (Oct.) 1944.

The middle of the presumptive neural plate of the late gastrula that has been transplanted into the blastema forms some epidermis and epidermal derivatives, as well as brain and eyes. In these transplants the ectoderm has been underlaid by chorda mesoderm for only a short time.

Ectoderm from the early gastrula forms epidermis and suckers, and occasionally nerve tissue and cartilage; horny jaws develop in about half the cases, especially when there is contact of the graft with the regenerating notochord of the host. Ectoderm from the middle gastrula develops like ectoderm from the early gastrula, but horny jaws are always formed, and often nasal sacs as well. Nasal sac competence must occur between the early and the middle gastrula stage and does not depend on the action of the archenteron roof. Ventral ectoderm of the late gastrula forms only epidermis, suckers and horny jaws. These results indicate a gradual chemodifferentiation within the ectoderm which is independent of the action of the chorda mesoderm.

Intestinal tubes with the mucosa toward the lumens are formed from the endodermal substratum of the ventral ectoderm from the late gastrula. The normal orientation of the gut mucosa is due to the surrounding blastema mesenchyme. As was expected, the ventral lip mesoderm forms celom, with visceral and parietal peritoneum and sometimes mesenteries.

REID, Boston.

PHASES IN REGENERATION OF THE URODELE LIMB AND THEIR DEPENDENCE UPON THE NERVOUS SYSTEM. OSCAR E. SCHOTTÉ and ELMER G. BUTLER, J. Exper. Zool. **97**:95 (Nov.) 1944.

The influence of nerves on regeneration of the limb of larvae of Amblystoma punctatum and Amblystoma opacum was studied in 252 larvae. To obtain comparable stages of regenerating limbs, temperature conditions and age of larvae were carefully controlled. Repeated resection of the brachial plexus insured permanent nervelessness of the limbs. Denervation occurred two to sixteen days after amputation.

The presence of nerves was found to be necessary for (*a*) the whole of the dedifferentiative phase which starts regeneration and establishes the blastema, and (*b*) the transformation of the young blastema into a regenerate with morphogenic determination. The presence of nerves was found unnecessary for growth and differentiation of the regenerate (phase of morphogenesis).

The nervous system is an important agent only for specifically regenerative activities; it is no more important for morphogenesis during regeneration than for morphogenesis in development of embryonic limbs.

REID, Boston.

THE BRAIN OF DROSOPHILA MELANOGASTER. MAXWELL E. POWER, J. Morphol. **72**:517 (May) 1943.

The finer anatomy of the brain of the wild type Drosophila melanogaster (Oregon R) was studied. using sectioned material stained by a modification of the Bodian silver impregnation technic.

The brain is a laterally elongate, compact body in which the protocerebrum, deutocerebrum and tritocerebrum are fused together. It has a cellular cortex and a fibrous core, which is organized into glomeruli: (*a*) the central complex, (*b*) a pair of corpora pedunculata, (*c*) the protocerebral bridge, (*d*) a pair of antennal glomeruli and (*e*) three pairs of optic glomeruli. These are connected with each other and with the general brain by tracts and commissures.

The central complex contains four glomeruli and is an association center, receiving fibers from several parts of the brain.

The corpora pedunculata, or mushroom bodies, are on either side of the central complex, and each is composed of three stalks, extending in different planes of orientation. These bodies are less well developed than those in other orders of insects.

The protocerebral bridge is a transverse cylinder located in the dorsoposterior portion of the brain. The bridge is an association center, being connected with the central complex, the optic tubercles, the antennal glomeruli and the general brain.

The antennal glomeruli (deutocerebrum) are located anteriorly and are connected by commissures above the esophagus. The largest fiber bundles are the olfactoria globularis tracts and the pair of large antennal nerves which are connected with the antennae.

The lateral portions of the brain are the optic lobes. each of which contains three optic glomeruli. The external glomerulus is separated from the middle glomerulus by the external chiasm (centripetal visual fibers). The internal glomerulus has an anterior and a posterior portion, which are connected with each other and with the middle glomerulus by the fibers of the internal chiasm. All connections between the optical system and the central portions of the brain are by way of the internal glomeruli. The middle glomeruli are connected with each other by a special commissure. There are five major tracts placing the inner glomeruli in communication with other parts of the brain.

The opposite sides of the protocerebrum proper are connected with each other by three major commissures. Extending through the protocerebrum, but belonging to the deutocerebrum, is the pair of olfactoria globularis tracts from the antennal glomeruli.

In addition, there are two median, unpaired tracts, each of which extends dorsoventrally and enters the subesophageal mass. One of these, the ocellar stalk, extends into the thoracic nervous center.

The cellular cortex is composed of cells of different sizes and shapes which are arranged on the surface of the brain with precise bilateral symmetry.

REID, Boston.

THE AFFERENT PATH OF THE PUPILLODILATOR REFLEX IN THE CAT. A. J. HARRIS, R. HODES and H. W. MAGOUN, J. Neurophysiol. **7**:231 (July) 1944.

Harris, Hodes and Magoun studied the dilatation of the pupil resulting from stimulation of the sciatic, splanchnic and trigeminal nerves and observed the responses to such stimulation after various lesions of the spinal cord and brain. The authors found that the reflex was mediated at the level of the midbrain, since the destruction of the brain above the oculomotor nucleus did not impair the response. A pathway common to all types of stimuli administered ascends through the lateral funiculus of the cord and the reticular formation of the medulla, lies in a paramedian position in the dorsal pontile tegmentum and ascends through the midbrain in or near the central gray matter. This pathway is distinct from the lateral spinothalamic tract.

FORSTER, Philadelphia.

## Physiology and Biochemistry

VARIATION IN CIRCULATORY AND RESPIRATORY RESPONSES TO CAROTID SINUS STIMULATION IN MAN. M. GALDSTON, R. GOLDSTEIN and J. M. STEELE, Am. Heart J. **26**:213 (Aug.) 1943.

Galdston and his associates review the history of research on stimulation of the carotid sinus, giving particular attention to the investigations of Weiss and his co-workers, who distinguished three types of syncope resulting from such stimulation. The first, in which syncope is accompanied with definite slowing of the heart rate or asystole and a consequent fall in arterial pressure, is designated the "vagal type"; the second, in which a pronounced fall in arterial pressure occurs without significant slowing of the heart, the "depressor type," and the third, in which there is syncope without either slowing of the heart or fall in arterial pressure, the "cerebral type." The authors studied the relationships, in point of time, of arterial pressure, pulse rate, venous pressure, respiration and onset of syncope and convulsions. One hundred persons were examined, 26 of whom presented a sensitive carotid sinus reflex. Of these, 17 regularly had convulsive seizures on stimulation of the carotid sinus. The common circulatory response in the 17 persons was slowing of the heart and asystole (vagal response), with a fall in arterial pressure (depressor response). A pure vagal response was next most common. A pure depressor response was not observed except when the patient was under the influence of atropine. Paredrine hydrobromide aqueous prevented to a large degree the depressor responses. Two patients had convulsions without significant circulatory change (cerebral type). In 3 other patients syncope and convulsions persisted when circulatory changes were inhibited by the administration of atropine or paredrine hydrobromide. Hyperpnea is the regular respiratory response to digital pressure in the region of the carotid tinus. Its occurrence is independent of the circulatory response. It is independent of age or sex. It is not prevented by barbiturate anesthesia, but local infiltration of the region about the carotid sinus and carotid body with procaine hydrochloride abolishes it. Prolonged stimulation is often followed by a phasic type of respiration similar to Cheyne-Stokes breathing. Evidence is presented that hyperpnea after pressure on the neck in the region of the carotid sinus in man may be caused by a disturbance of the blood supply to the carotid body rather than by mechanical stimulation of the carotid sinus.

J. A. M. A.

THE EFFECT OF INTRAVENOUS INJECTION OF EPINEPHRIN AND ANGIOTONIN BEFORE AND AFTER THE PRODUCTION OF NEUROGENIC HYPERTENSION. CAROLINE BEDELL THOMAS and ROSS L. MCLEAN, Bull. Johns Hopkins Hosp. **75**:319 (Nov.) 1944.

Thomas and McLean report on the effect of intravenous injections of epinephrine and angiotonin on 3 unanesthetized dogs before section of the moderator nerve and when hypertension was present. The observations show that pressor responses to epinephrine and angiotonin are not significantly altered by the induction of neurogenic hypertension. Angiotonin produces a marked cardiac acceleration in the hypertensive animal, whereas it slows the cardiac rate slightly when the dog is in the normal state. Epinephrine has a similar, but less pronounced, effect on the heart rate.

These data indicate that while peripheral vasoconstrictor activity may be increased in the case of neurogenic hypertension, vasoconstrictor tone is not sufficiently great to interfere with the action of either sympathicomimetic or humoral vasoconstrictor substances. Angiotonin stimulates the cardioaccelerator mechanism, but this effect is normally masked by the moderator reflexes.

GUTTMAN, Philadelphia.

LACTIC ACID OXIDATION QUOTIENT IN MINCED BRAIN OF NORMAL AND AVITAMINOTIC CHICKEN. P. E. GALVÃO, J. PEREIRA and J. P. LIMONGI, J. Biol. Chem. **157**:667, 1945.

Few data are available on the quotient of lactic acid oxidation, i. e., lactic acid removed/lactic acid oxidized, in the central nervous system. Determination of the quotient of lactic acid oxidation in the brain of birds seemed particularly interesting because these animals show a disturbance in the oxidation of lactic acid in specific regions of the central nervous system. With birds exhibiting pronounced symptoms of $B_1$ avitaminosis, the decreased oxidation of the lactic acid formerly noted for the brain stem was not accompanied with an impaired removal of lactate. The quotient of lactic acid oxidation, therefore, increased. Addition of thiamine hydrochloride produced partial restoration of the oxidation of lactate without significant influence on the removal of lactate; the quotient, consequently, tended toward normal. In the present experiments the nerve tissue was finely minced. This treatment brought about results substantially different from those obtained with thoroughly ground tissue used in the previous experiments. In the brain stem of avitaminotic chickens a great diminution of extra oxygen was accompanied with a considerable, though smaller, reduction in removal of lactate; consequently, the oxidation quotient tended to rise. Addition of thiamine hydrochloride, besides promoting the extra oxygen uptake, increased removal of lactate. No differences were found between normal cerebrum and the cerebrum of birds with $B_1$ avitaminosis.

PAGE, Cleveland.

FUNCTIONAL DIFFERENTIATION IN EMBRYONIC DEVELOPMENT: I. CHOLINESTERASE ACTIVITY OF INDUCED NEURAL STRUCTURES IN AMBLYSTOMA PUNCTATUM. EDGAR J. BOELL and SHIH-CHANG SHEN, J. Exper. Zool. **97**:21 (Oct.) 1944.

Boell and Shen determined the cholinesterase content of various tissues in developing embryos of Amblystoma punctatum with a modified ultramicromanometric technic. At the period of the closing of the neural folds there was a significant localization of cholinesterase in the nervous system, as compared with the amount in the ectoderm. The concentration of cholinesterase be-

came progressively greater as the nervous system differentiated.

The cholinesterase activity of secondary, induced, neural structures, produced by the action of implanted chorda mesoderm on competent ectoderm, is of the same order of magnitude as that of the primary neural tissues of the host. Ectoderm which has not received the stimulus of the inductor has a much lower cholinesterase value.

Apparently, induction, in addition to causing the development of distinct morphologic changes, stimulates the induced tissue to develop the characteristic biochemical machinery of normal nerve tissue. The authors suggest that the cholinesterase content of secondary, induced, neural structures may be considered as a measure of their potential or incipient functional differentiation.

REID, Boston.

LIMB PARAMETERS AND REGRESSION RATES IN DENERVATED AMPUTATED LIMBS OF URODELE LARVAE. OSCAR E. SCHOTTÉ and ALEXANDER G. KARCZMAR, J. Exper. Zool. **97**:43 (Oct.) 1944.

The regression in denervated amputated limbs of Amblystoma and Triturus larvae (18 to 48 mm.) was studied under constant temperature conditions (16 and 20 C.). Regression rates were obtained from measurements of camera lucida drawings made at regular intervals and expressed in microns per hour for the absolute individual regression rate, or referred to the initial length of the stump and expressed in per cent per hour for the relative individual regression rate. Regression rates presented remarkable fluctuations, which were correlated with the dimensions of the regressing limbs.

Comparison of relative individual regression rates in long and in short limbs showed that long limbs exhibit slower regression rates than short limbs and that the rates are independent of anatomic levels.

The general trend of regression rates is determined by the activities of the dedifferentiation phase, while the variability of these rates is conditioned by the volumes of limb material available. Thick limbs regress with slow rates; thin limbs, with high rates; medium-sized limbs, with average rates. Since the volume removed is directly proportional to the cross section area of the limb, the cross section area (width parameter) of the limb appears to be the controlling agent of the disposal phase. This is especially striking in thin limbs.

The heterogeneity of histologic structures in denervated amputated limbs influences the two phases of regression. Bone, cartilage and tendons resist the regression process more than do the soft tissues of the limb.

At present the regression effect appears to be the result of an interplay of three factors: (*a*) availability of materials, determined by the limb dimensions and subject to the activities of the dedifferentiation phase; (*b*) a limiting factor, the disposal phase, controlled by the width parameter of the limb, and (*c*) a modifying factor, determined by the biochemical and biophysical nature of the regressing tissues and conditioned by the physiologic age of the denervated amputated limb.

REID, Boston.

THE FORMATION OF ACETYLCHOLINE: A NEW ENZYME: "CHOLINE ACETYLASE." D. NACHMANSOHN and A. L. MACHADO, J. Neurophysiol. **6**:397 (Sept.-Nov.) 1943.

Nachmansohn and Machado extracted an enzyme which forms acetylcholine from the brains of various species and from the electric organ of Electrophorus electricus. This enzyme they named choline acetylase. The formation of acetylcholine by this enzyme occurs only in the presence of adenosine triphosphate. Fluoride enhances the formation of acetylcholine. According to Ochoa, fluoride inhibits adenosine triphosphate but not the transfer of phosphate to a phosphate acceptor. Potassium and ammonium ions within certain concentrations do not affect the enzyme, while copper, iodoacetic acid and iodine strongly inhibit the activity of the enzyme.

FORSTER, Philadelphia.

AN ANALYSIS OF THE VARIABILITY OF SPINAL REFLEX THRESHOLDS. J. S. DENSLOW, J. Neurophysiol. **7**:207 (July) 1944.

Denslow studied the thresholds of reflex muscle contraction on applying moving pressure stimuli to the spinous processes. The thresholds were found to be relatively constant in a given subject, with wide variations in thresholds in different subjects and with variations from segment to segment, and even from side to side, in the same subject. These differences may be due to (1) change in environment of deep pressure or stretch receptors in areas of medium and high threshold levels and to a change in that of other endings in low threshold areas and (2) to an imbalance of excitor-inhibitor influences, such as may occur in an enduring subliminal central excitatory state. Denslow found the mean threshold to be slightly higher on the left side of the body than on the right. He concludes that in the absence of organic disease, thresholds for reflex muscle contraction might provide a neurologic index of the efficiency of the organism in coping with mechanical weaknesses and with environmental stresses.

FORSTER, Philadelphia.

PARASYMPATHETIC REGULATION OF HIGH POTENTIAL IN THE ELECTROENCEPHALOGRAM. CHESTER W. DARROW, JOHN R. GREEN, EDWARD W. DAVIS and HUGH W. GAROL, J. Neurophysiol. **7**:217 (July) 1944.

Darrow, Green, Davis and Garol sectioned the facial nerves of cats so as to interrupt the parasympathetic pathways to the pial blood vessels. The animals were curarized and placed under artificial respiration. Under these conditions hyperventilation produced high potential, slow and spiked activity of the cerebral cortex. These alterations of potential could be abolished by stimulation of the peripheral cut end of the facial nerve or by the intravenous administration of physostigmine, whereas the application of atropine enhanced the response. The authors conclude that a parasympathetic influence on the electrical activity of the brain has been demonstrated and that a cholinergic influence on cerebral metabolism and circulation is implied. The homeostatic regulation of cerebral circulation is probably through a supplemental relationship between acetylcholine and carbon dioxide.

FORSTER, Philadelphia.

CHANGES OF WEIGHT AND NEUROMUSCULAR TRANSMISSION IN MUSCLES OF IMMOBILIZED JOINTS. P. THOMSEN and J. V. LUCO, J. Neurophysiol. **7**:245 (July) 1944.

Thomsen and Luco studied the effects of fixation of the tibiotarsal joint on the neuromuscular synapse and the weight of the soleus and tibialis anticus muscles of cats. Fixation of the joint was in hyperextension, in hyperflexion or in midposition. Alterations in neuro-

muscular transmission after these fixations were the same as after tenotomy. Moreover, the immobilized muscles, like tenotomized muscles, were less sensitive to curare. Fixation in hyperflexion up to fourteen days resulted in an increase in the weight of the soleus and a decrease in the weight of the tibialis, while the converse was obtained with fixation in hyperextension. The authors conclude that in immobilization, as in tenotomy, the abnormal tension to which the muscle is exposed produces the neuromuscular changes through a reflex mechanism.

FORSTER, Philadelphia.

RELATION OF CEREBRAL CORTEX TO SPASTICITY AND FLACCIDITY. W. KEASLEY WELCH and MARGARET A. KENNARD, J. Neurophysiol. **7**:255 (Sept.) 1944.

Welch and Kennard studied in primates the spasticity and flaccidity resulting from ablations of various areas, either singly or in combination. They confirmed the observations of other investigators on the effects of primary ablations. Removal of area 6, with area 4s, was followed by moderate spastic paresis. Removal of area 4 yielded paresis without spasticity. Removal of the postcentral gyrus resulted in transient flaccidity with some paresis.

Welch and Kennard studied the effects of successive removals of the areas in question. The ablation of areas 4, 4s and 6, either simultaneously or seriatim, resulted in immediate spastic paresis. When ablations had resulted in spasticity, subsequent ablation of the postcentral gyrus increased the paresis and in monkeys usually increased spasticity, while in chimpanzees the increase of spasticity was definite. Ablation of area 4 and the postcentral gyrus resulted in spasticity. Ablation of any contralateral motor area in addition to a primary lesion causing spasticity increased the spasticity. In the monkey, when the entire hemisphere was ablated, removal of areas 4 and 6 augmented the spasticity and paresis to a greater degree than did ablation of the postcentral gyrus.

FORSTER, Philadelphia.

ACUTE AND CHRONIC PARIETAL LOBE ABLATIONS IN MONKEYS. TALMADGE L. PEELE, J. Neurophysiol. **7**:269 (Sept.) 1944.

Peele studied the effects of removal of the various cytoarchitectural areas of the parietal lobe of the macaque monkey. Removal of area 3, areas 1 and 2, area 5 or area 7 individually or of areas 1-2, 5 and 7 in combination did not result in paralysis, although the animals were loath to move. Removal of area 3 or of areas 1 and 2 affected the arm and the leg equally, while removal of area 5 affected the leg, and removal of area 7 the arm, particularly. This differential localization was found to be compatible with the distribution of the parietospinal fibers. Hypotonia was consistently present and was more marked proximally. The hypotonia probably accounted for the resting posture of the animals and for the ataxia and slowness of movement. The tendon reflexes exhibited increased threshold, slowness of execution and increased excursion. Tactile and painful stimuli were not as well appreciated after ablations, and localization of stimuli was impossible. Placing and hopping responses were immediately impaired but returned in three weeks, while tactile placing was permanently impaired with postcentral lesions. Muscular atrophy and hyperpathia occurred in 1 animal. The postcentral gyrus appeared essential for recognition of tactile and painful stimuli, and all parietal areas were necessary for localization and discrimination.

FORSTER, Philadelphia.

CEREBRAL METABOLISM IN EXPERIMENTAL HEAD INJURY. E. S. GURDJIAN, J. E. WEBSTER and W. E. STONE, War Med. **6**:173 (Sept.) 1944.

Gurdjian, Webster and Stone found that the oxygen saturation of arterial blood was frequently increased after experimental head injury in dogs. In a few instances there was a decrease. Variations in respiratory function govern the changes. The cerebral arteriovenous differences in oxygen, carbon dioxide and glucose did not change appreciably as a result of injury to the head. The differences were calculated with blood obtained from the femoral artery and from the sagittal sinus.

Areas of contusion showed increased levels of lactic acid and inorganic phosphate and decreased levels of phosphocreatine and adenosine triphosphate. These changes may be due to a combination of direct injury to the cells and anoxia resulting from vascular damage.

In unbruised areas of the cortex, the chemical constituents studied were frequently entirely normal, even in profoundly injured animals. This was thought to signify that in a great many animals there was no evidence of a generalized disturbance in cerebral oxidations. In a few dogs there was increase in lactic acid in the presence of adequate arterial oxygen. This may represent either a mild degree of local damage or a more widespread disturbance in cerebral oxidative mechanisms in these animals.

Impaired oxidative mechanisms may occur in localized areas of the cortex without significant changes in cerebral arteriovenous differences in oxygen, carbon dioxide or glucose.

Improvement occurs in the oxidative processes in areas of contusion during a two day recovery period, as evidenced by return toward normal levels of the chemical constituents studied.

Although administration of oxygen induces no striking acceleration of recovery processes, the results seem to indicate a trend toward better recovery with high intake of oxygen.

PEARSON, Philadelphia.

A COMPARISON OF ALTITUDE AND EXERCISE WITH RESPECT TO DECOMPRESSION SICKNESS. S. F. COOK, O. L. WILLIAMS, W. R. LYONS and J. H. LAWRENCE, War Med. **6**:182 (Sept.) 1944.

Four groups of healthy young men (aged 18 to 20) were given two chamber tests each. One group performed a standard exercise at 30,000 feet (9,150 meters) every five minutes for ninety minutes; the exercise consisting of ten 9 inch (23 cm.) step-ups in thirty seconds. The second group performed the same exercise every two and one-half minutes at the same altitude. The third group performed the standard exercise every five minutes at 38,000 feet (11,500 meters), and the fourth group performed the exercise every two and one-half minutes at 38,000 feet. The following criteria were used in comparing the bends-inducing effect of the four sets of conditions: the per cent incidence of symptoms, per cent incapacitation, time of onset of symptoms, time of descent, maximum intensity of symptoms and velocity of development of symptoms. All criteria showed statistically significant differences between the two altitudes with constant exercise. When the altitude was held constant at 30,000 feet, the effect of doubling the frequency of the standard exercise was relatively slight and not of statistical significance in all cases. At 38,000 feet, the effect of increase of exercise was significant with most criteria but was much less pronounced than the effect of changing altitude.

In general, the conclusion may be drawn that an increase in altitude from 30,000 to 38,000 feet increases the incidence and severity of decompression sickness considerably more than doubling the muscular work done by means of the step-up exercise.

PEARSON, Philadelphia.

EXPERIMENTAL PRODUCTION OF MOTION SICKNESS. E. A. SPIEGEL, M. J. OPPENHEIMER, G. C. HENNY and H. T. WYCIS, War Med. **6**:283 (Nov.) 1944.

The authors tested a number of medical students on a rotating-tilting machine. Symptoms of motion sickness were produced within eight minutes in 75 per cent of unselected subjects. The weaker method of stimulation (rotation combined with sagittal movements of the head or body) was sufficient to reveal a high degree of susceptibility. The stronger stimulation (rotation combined with frontal head movements preceding or succeeding rotation combined with sagittal head movements) was effective in nearly all moderately susceptible persons and produced symptoms even in some of the subjects who were supposedly not susceptible according to previous experience.

Optic fixation of an object that participates in all movements of the head tends to diminish the incidence of motion sickness as compared with the effect of stationary objects of the surroundings watched by the subject.

Typical illusions of spatial orientation were produced. Their appearance was independent of that of the vegetative symptoms of motion sickness, indicating the presence of two rather independent mechanisms.

Symptoms of motion sickness may be elicited not only by stimulation of the maculas but by stimuli acting on the cristae ampullares.

PEARSON, Philadelphia.

ACUTE HIGH ALTITUDE ANOXIA. R. A. KRITZLER, War Med. **6**:369 (Dec.) 1944.

A study was made of the observations at necropsy in 27 cases of acute high altitude anoxia. Widespread, severe capillary congestion was found. This was constant in the pulmonary, renal, intestinal and cerebral capillaries. The skeletal muscle failed to reveal congestion. In a high proportion of cases the systemic venous and portal circulations showed gross and microscopic congestion, and the right ventricle was dilated. There was wide individual variation in the incidence, location and amount of edema and hemorrhage. An exception to this was the consistent occurrence of hemorrhage in the thymus and in the middle ears. Swelling of endothelial cells of capillaries of the renal medulla was observed. Fat-free and glycogen-free vacuoles were found in the myocardium and liver and less frequently in cells of other organs.

PEARSON, Philadelphia.

PYRAMIDAL SECTION IN THE CAT. E. G. T. LIDDELL and C. G. PHILLIPS, Brain **67**:1, 1944.

Liddell and Phillips studied 34 cats in which the pyramidal tract had been sectioned by an approach through the basioccipital bone with sterile technic. The medulla was subsequently studied in serial sections. Unilateral section of the pyramidal tract produced immediate paresis of the contralateral limbs with scissoring, defective hopping and placing reactions and weakness in flexion of the forepaw. The paresis cleared up in several days, but for the duration of observations (twelve months) placing and hopping were impaired. The affected hindlimb when unsupported showed a tendency to extension of the solid, long-resisting type without clasp knife effect. This hypertonia of the extensor muscles decreased somewhat from the second to the sixth week. Walking on a horizontal ladder demonstrated the hypertonia well. Pyramidal section which was incomplete or was so extensive that it involved the medial fillet or the olive produced less hypertonia. The knee jerk in the affected extremities was brisk and of extensor type. Section of both pyramidal tracts produced a bilateral picture of the type described for unilateral section. The horizontal ladder test revealed the animal to be immobile.

FORSTER, Philadelphia.

FIBRE INTERACTION IN INJURED OR COMPRESSED REGION OF NERVE. RAGNAR GRANIT, LARS LEKSELL and C. R. SKOGLUND, Brain **67**:125, 1944.

Granit, Leksell and Skoglund studied the activity of the sciatic nerve induced by stimuli administered to a component motor or sensory root. To avoid the back response observed by Lloyd, it was necessary completely to denervate the limb. The authors found that under these conditions an electrical response could be elicited when a stimulus was administered to the motor root or to the sensory root and recordings were obtained from the other root. The responses were of greater amplitude when read from the sensory root and the stimulus was applied to the motor root. When recordings were taken from the sciatic nerve and the stimulus was administered to a sensory root, the usual nerve impulse was obtained, followed by a small wave traveling in the opposite direction. This wave was transmitted by an "artificial synapse," due to fiber interaction at the site of section of the sciatic nerve. Like other synapses, this artificial synapse was susceptible to anesthetics and anoxia. Fresh sectioning of a nerve increased the transmission at the artificial synapse for a period of five to ten minutes. Crushing the sciatic nerve with a ligature was as effective as direct sectioning of the nerve. Moderate pressure could produce the same response. In some instances sectioning the popliteal nerve augmented responses begun in the peroneal nerve. The authors concluded that sensory fibers have less capacity to resist stimulation and that since this is particularly true of pain fibers of the so-called C group, this fiber interaction may be of importance in the explanation of causalgia.

FORSTER, Philadelphia.

INVESTIGATIONS ON MUSCLE ATROPHIES ARISING FROM DISUSE AND TENOTOMY. J. C. ECCLES, J. Physiol. **103**:253, 1944.

Eccles studied atrophy in inactivated and/or tenotomized muscles in 30 cats. The loss of weight and the response to stimulation were observed. The latter was recorded as the ratio of the maximum tetanic contraction to the weight of the muscle or as the ratio of the maximum tetanic contraction to the maximum twitch contraction. The muscles of the hindlimbs were studied after inactivation through isolation of the lumbar portion of the spinal cord and section of the dorsal roots in the same area. Muscles innervated by the isolated spinal segment generally showed no activity, though fibrillation appeared in some specimens.

It had previously been shown that in such preparations daily tetanization of the sciatic nerve largely prevented loss of weight in the flexor muscles of the ankle joint but was much less effective in the extensor muscles. Because of the greater power of the flexor muscles, they were able to shorten maximally during

stimulation, whereas the extensors were stretched. The influence on muscle atrophy of this difference in length during stimulation was investigated by means of preparations in which appropriate tendons were severed or the ankle joint forcibly held in the desired position. The results of these experiments showed that the greater the length of the muscle during therapeutic stimulation, the better the results with regard to maintenance of weight; however, the reverse was true with regard to the maintenance of response to tetanic stimulation. The results were particularly striking in the flexor muscles but applied in some degree to the extensors. It was found that even under identical mechanical conditions the weight of the flexor muscle was better maintained by daily stimulation of the nerve than was that of the extensor muscle. Consequently, some other unknown factor was involved in the differences in response to therapeutic stimulation of the two groups of muscles.

The influence of shortening on muscle atrophy was further studied by means of tenotomy alone, leaving the nerves intact. Tenotomized muscles undergo maximal shortening and likewise undergo atrophy corresponding to that of disused muscles, The author believes that the atrophy is a result of the excessive shortening. He points out that the most satisfactory condition for preventing atrophy in disused muscle is that in which the muscle shortens against a load during therapeutic stimulation. This conclusion applies both to flexor and to extensor muscles. The one effective treatment for tenotomized muscle is immediate suture of the tendon, since therapeutic stimulation is ineffective in preventing atrophic changes and aggravates the excessive shortening of the muscle.

THOMAS, Philadelphia.

THE INHIBITION OF HISTAMINE RELEASE BY A PITUITARY-ADRENAL MECHANISM. G. UNGAR, J. Physiol. **103**:333, 1944.

Previous observations of Gotzl and Dragstedt have shown that the blood of normal rabbits when mixed with peptone in vitro releases considerable amounts of histamine. Ungar confirmed these observations in guinea pigs and rats. He found, further, that this reaction was prevented by previous exposure of the animals to sublethal shock due to peptone, trauma or anaphylaxis. The protection against the release of histamine in the presence of peptone can be passively transferred by the injection of serum of previously traumatized animals into the test animals. Apparently, trauma causes the release into the blood of a substance which protects against the release of histamine in the presence of peptone. This protecting agent was absent from the serum of traumatized animals which had been adrenalectomized or hypophysectomized. The author concludes that trauma stimulates the pituitary gland to release a substance which, acting through the adrenal gland, protects against peptone shock. He points out that histamine is probably not the only substance released in the blood in the presence of peptone. Histamine was selected for study because of the ease with which it can be estimated quantitatively.

THOMAS, Philadelphia.

## Neuropathology

PATHOLOGY OF CONVALESCENT POLIOMYELITIS IN MAN. J. H. PEERS, Am. J. Path. **19**:673 (July) 1943.

Peers describes the pathologic aspect of the residual lesions of 3 patients with poliomyelitis who had survived seven, five and eighteen and one-half weeks from the onset of illness. Lesions in the cerebral cortex, consisting of perivascular collars of lymphoid cells and interstitial foci of microglia and astrocytes, were confined to the paracentral lobules. Only minimal lesions were observed in the basal ganglia and thalamus. In the midbrain the substantia nigra presented the most severe damage. Lesions in the pons were confined to the tegmentum. Loss of nerve cells was extensive in Deiters' nuclei and more patchy and asymmetric in the motor fifth and seventh nuclei. Single necrotic cells were still present four months after the acute illness. Perivascular infiltration diminished, and the density of fibrous gliosis increased with the duration of convalescence. In the cerebellum, lesions were encountered only in the tectal nuclei and in the cortex of the vermis. The most prominent changes in the medulla consisted of loss of cells and scarring in the reticular substance similar to that present in the pons. The spinal cord presented an almost complete loss of nerve cells throughout the entire length of the anterior gray substance. In contrast, the lateral horns were comparatively spared; lesions in Clarke's column were patchy and asymmetric, and no definite changes appeared in the posterior horns. Replacement gliosis in the anterior horns was at first abundant but delicate, with bulky astrocytes. Later the cells shrank, and the fibrils became coarser. In the white matter of the spinal cord there was mild diffuse demyelination of most of the ventral and lateral columns with the exception of the pyramidal tracts. In the posterior columns demyelination was partial and was confined to the region of the comma tracts of Schultze. The anterior nerve roots showed severe degeneration consequent to the extensive loss of anterior horn cells. Almost all the coarse motor fibers had disappeared. In contrast, the fine myelinated efferent sympathetic fibers were mostly spared. In the gasserian, dorsal root and sympathetic ganglia there were a few small foci of lymphoid cells. In the root ganglia only rare cells had disappeared, leaving behind capsules filled with mononuclear cells. The meninges contained only a few scanty foci of lymphoid cells, and no lesions were seen in the choroid plexus.

J. A. M. A.

CHANGES IN THYMUS WITH SPECIAL REFERENCE TO MYASTHENIA GRAVIS. F. HOMBURGER, Arch. Path. **36**:371 (Oct.) 1943.

Homburger reports that among 6,000 autopsies performed at the New Haven Hospital 41 instances of tumor or of enlargement of the thymus were encountered. In 27 of these the patients were children under 16 years of age. The remaining 14 cases include 3 of cancer, 3 of enlargement of the gland associated with thyrotoxicosis, 6 of enlargement of the gland encountered incidentally at necropsy and 2 of noncancerous thymic tumor coincident with myasthenia gravis. Epithelial metaplasia was a prominent feature and was accompanied by scarcity of the corpuscles of Hassall in the 2 thymic tumors associated with myasthenia gravis. This observation is in accordance with the conclusions of Bell, Lievre and Norris that thymic tumors in patients with myasthenia gravis are of a distinct type characterized by epithelial metaplasia; it is in contradiction to the more recent opinion stated by Obiditsch and Sloan, who stressed the predominance of lymphoid tissue in thymic tumors of patients with myasthenia gravis.

J. A. M. A.

INTRACRANIAL LIPOMA. A. R. VONDERAHE and W. T. NIEMER, J. Neuropath. & Exper. Neurol. **3**:344 (Oct.) 1944.

Vonderahe and Niemer report 4 cases in which an unsuspected intracranial lipoma was found at autopsy. This tumor is usually small and well circumscribed, but invasion occurs in some instances. The tuberal and quadrigeminal regions, the infundibulum and the dorsal surface of the corpus callosum are the most frequent sites of this neoplasm.

Three of the tumors described here were found between the infundibulotuberal region and the mamillary bodies. One of them possessed a pedicle which penetrated the infundibulum. A fourth tumor invaded the right inferior quadrigeminal body and the anterior medullary velum. Two of the tumors were hemangiomatous in type, and one contained a collection of bipolar neurons.

Vonderahe and Niemer state that lipomas which develop some time after gastrulation contain only adipose tissue; others, developing shortly after gastrulation, possess more highly differentiated mesodermal derivatives, such as bone; still others, developing before or during gastrulation, possess neuroectodermal as well as mesodermal elements. There is thus a transition from simple lipoma to the more complex teratoid tumor and teratoma.

GUTTMAN, Philadelphia.

KERNICTERUS UNASSOCIATED WITH ERYTHROBLASTOSIS FETALIS. FRANCIS M. FOSTER and RAYMOND A. MCCORMACK, J. Neuropath. & Exper. Neurol. **3**: 379 (Oct.) 1944.

Foster and McCormack report their studies on 2 patients with kernicterus. In 1 Negro male infant severe jaundice developed thirty-six hours after delivery, followed by opisthotonos and rigidity. He died five days after birth. The parents were healthy, and the three preceding pregnancies had resulted in three viable female children. Both parents were Rh positive. The other Negro male infant, a first born of syphilitic parents, presented severe jaundice on the fourteenth day and died on the fifteenth day. The mother had received antisyphilitic therapy, beginning in the sixth month of pregnancy. Both parents were Rh positive. Necropsy was performed in both cases.

Foster and McCormack state that the cause of the severe icterus of the newborn in these 2 cases is not evident. Erythroblastosis fetalis is ruled out by serologic studies, blood smears and autopsy.

GUTTMAN, Philadelphia.

THE CENTRAL NERVOUS SYSTEM IN PORPHYRIA. A. B. BAKER and C. J. WATSON, J. Neuropath. & Exper. Neurol. **4**:68 (Jan.) 1945.

Baker and Watson report the case of a 24 year old man in whom pain developed in the extremities and abdomen, followed within three weeks by flaccid quadriplegia, restlessness, irritability and, at times, impulsiveness. Speech was thick; there was some dysphagia. Facial diplegia was present, and the tongue deviated to the left. A diagnosis of acute idiopathic porphyria was finally established, and laboratory studies revealed porphyrinuria. The diagnosis was delayed because of the normal color of the freshly voided urine. A history of voiding red urine intermittently for one year and of mild photosensitivity with minimal formation of vesicles during the summer was obtained. A remission occurred, but about two and a half years later there was a final acute exacerbation, associated with voiding of reddish brown urine. The urine gave a strong reaction for porphobilinogen, in addition to zinc uroporphyrin and a fair amount of porphobilin. In a few weeks bulbar involvement occurred, and two months later death ensued.

Necropsy showed no gross abnormalities in the nervous system. Microscopic study revealed evidence of alterations in the neurons and myelin sheaths throughout the brain and the spinal cord, in addition to extensive destruction in the peripheral nerves. The intracranial lesions, though scattered, appeared to be most severe within selected nuclei of the cranial nerves, namely, the nuclei of the facial and hypoglossal nerves and the dorsal nucleus of the vagus nerve.

The role of porphyrins in the production of lesions of the nervous system is not clear. Some studies indicate that, while porphobilinogen itself is innocuous, some pigment derived from it (other than uroporphyrin) may be the substance which is active in producing the nervous manifestations and possibly, also, the abdominal colic.

GUTTMAN, Philadelphia.

A DISTINCTIVE TYPE OF ENCEPHALOMYELITIS OCCURRING AMONG TROOPS IN THE NORTHERN TERRITORY OF AUSTRALIA. JOHN P. HORAN, GEORGE A. W. JOHNSTON, JOHN H. HALLIDAY, J. O'BRIEN and E. WESTON HURST, Brain **67**:93, 1944.

The authors report in detail 2 fatal cases of a previously undescribed type of encephalomyelitis. The first patient had lacerated his left little finger, after which he had a two weeks' illness, thought to have been acute polyarthritis. There developed pain in the left wrist, tenderness of the left ulnar nerve and transient sensory impairment in the distribution of that nerve. Two months after the onset, fever, chilliness, vomiting and headache developed, and the symptoms in the left hand became more severe. At this time he had definite atrophy of muscles supplied by the ulnar nerve. In the course of four days there developed numbness, tingling and weakness of the left leg and nuchal rigidity. The spinal fluid contained 633 cells per cubic millimeter, with a total protein content of 70 to 80 mg. per hundred cubic centimeters. During the ensuing two days he had numbness of the left side of the chest, facial paresis, inability to swallow and dysarthria, and death occurred, as a result of respiratory distress. Pathologic examination revealed that the ulnar nerve was degenerated; both the parenchyma and the sheath had been invaded by leukocytes. The meninges were infiltrated with mononuclear leukocytes. The parenchyma of the central nervous system contained large, sharply demarcated focal necroses, some of which were perivenous. These areas of necrosis contained masses of leukocytes, mixed leukocytes and pleomorphic microglia cells or microglia cells with a few lymphocytes and plasma cells. There was also evidence of diffuse leukocytic infiltration of the parenchyma and microglial proliferation. Alterations of the parenchyma of the central nervous system were most conspicuous in the spinal cord, while the changes in the brain stem and the cerebellum were at an earlier stage. The parenchyma of the cerebrum was not involved. Attempts to culture organisms or a virus were futile.

The second patient had a febrile illness seven days after a tonsillectomy with vomiting and headache, followed after two weeks by diplopia. He had a whitish yellow membrane over the tonsillar region and meningeal signs. The spinal fluid contained 250 lymphocytes per cubic millimeter. Pathologic examination revealed lesions identical histologically with those in the preceding case, occurring in the brain stem and the cerebellum.

The authors conclude that the pathogenic agent entered peripherally in each case and traveled along nerve paths to reach the central nervous system.

FORSTER, Philadelphia.

## Psychiatry and Psychopathology

A REVIEW OF CASES OF VETERANS OF WORLD WAR II DISCHARGED WITH NEUROPSYCHIATRIC DIAGNOSES. CHARLES B. HUBER, Am. J. Psychiat. **100**:306 (Nov.) 1943.

Huber studied 100 veterans of World War II, all of whom had been discharged for neuropsychiatric reasons. In 99 per cent of cases he felt the precipitating factor could not be considered the stress or strain of actual combat. No outstanding single feature could be found in the family or the personal histories. In some patients, particularly those of the psychoneurotic group, it is possible that the change in environment may have contributed to the onset of the illness. Venereal disease did not play an important role. Huber felt that many of the men could have been rejected prior to induction had proper notation been made of educational advantages.

FORSTER, Philadelphia.

ENURESIS IN THE NAVY. ALEXANDER LEVINE, Am. J. Psychiat. **100**:320 (Nov.) 1943.

Levine studied 150 instances of enuresis occurring among naval recruits. He concluded that enuresis was in itself only a symptom and that it was frequently associated with other symptoms indicative of a deep-seated personality disturbance. The affected men were usually immature, maladjusted and emotionally unstable. The siblings and parents of these patients presented numerous psychiatric abnormalities. In a high proportion of the patients there was present a lack of security, allowing for the persistence of infantile traits.

FORSTER, Philadelphia.

A STUDY OF FORTY MALE PSYCHOPATHIC PERSONALITIES BEFORE, DURING AND AFTER HOSPITALIZATION. W. LYNWOOD HEAVER, Am. J. Psychiat. **100**:342 (Nov.) 1943.

Heaver studied 40 males with psychopathic personalities. The diagnostic criteria of Cheney were followed. The average duration of illness was six and three-fourths months. One-half the group had forbears with psychopathic traits, and only 2 had well adjusted mothers. In over one-half the group the home environment was featured by environmental stress. In only 12 instances was a deep insight into the problem achieved. Therapy consisted in a well organized regimen, in addition to psychotherapy. On discharge, the condition of 36 of the 40 patients had improved. Follow-up studies on 31 of the 40 patients revealed that 23 had in some measure become acceptable to society and 16 could be considered as recovered.

Heaver concludes that the pathogenesis of psychopathic personality depends on an infantile pattern of conduct perpetuated unintentionally by parents with unconscious immaturity. Under these conditions emotional adequacy does not develop. The plastic mind of the child is conditioned by uncritical maternal devotion, and he fails to identify himself with his father. On the basis of this arises a protest against his own sex, leading to asocial behavior. The prognosis depends not on the duration of symptoms but on the gravity and dimensions of the conflict nucleus and the ability to compromise. The therapy of the psychopathic personality and of his family remains a challenge to psychiatry.

FORSTER, Philadelphia.

IMMEDIATE AND FOLLOW-UP RESULTS OF ELECTROSHOCK TREATMENT. LAUREN H. SMITH, DONALD W. HASTINGS and JOSEPH HUGHES, Am. J. Psychiat. **100**:351 (Nov.) 1943.

Smith, Hastings and Hughes studied the effects of electric shock therapy administered over a two year period to 279 patients. They concluded that this method is effective in the therapy of involutional melancholia and manic-depressive psychosis. Manic patients were found not to maintain their recovery as well as agitated and depressed patients. There is no evidence that electric shock either prevents a future psychotic attack or interferes with spontaneous clinical recovery. Electric shock was found to be ineffectual in treatment of schizophrenia and of doubtful value in treatment of the psychoneuroses. The use of curare-like medication decreased the incidence of traumatic skeletal injuries. While memory changes always occur during the course of therapy, they do not appear to be permanent.

FORSTER, Philadelphia.

FATAL CATATONIA. OTTO BILLIG and W. T. FREEMAN. Am. J. Psychiat. **100**:633 (March) 1944.

Billig and Freeman describe 3 cases of fatal catatonia, all occurring in females with schizophrenia. On the basis of their observations, as well as those reported in the literature, the authors conclude that fatal catatonia is a complication of the usual schizophrenic illness and does not constitute a separate form of the disease. It may occur in apparently healthy persons or appear as an exacerbation in the course of any form of schizophrenia. Prior to the onset of fatal catatonia there is a prodromal phase, lasting from two weeks to several months during which the usual schizophrenic pattern is displayed. The actual catatonic phase may be divided into two subphases: (1) a period of increasing perplexity, anxiety, incoherence and restlessness, associated with a blind drive toward annihilation, suicidal tendencies, acrocyanosis and hypertension, and (2) a phase in which motor restlessness becomes more primitive, consciousness becomes clouded, the blood picture changes, the temperature rises, the blood pressure falls, the pulse becomes weak and rapid, the pupils dilate and the reflexes disappear. Cyanosis appears; there are petechial hemorrhages into the tissues, and respiratory or vasomotor collapse occurs. At autopsy only petechial hemorrhages into the skin and erythropoiesis of the bone marrow are found. Billig and Freeman believe that changes in the hormonal-vegetative system may be responsible for the condition.

FORSTER, Philadelphia.

ANOREXIA NERVOSA: METABOLISM AND ITS RELATION TO PSYCHOPATHOLOGIC REACTIONS. S. M. SMALL and A. T. MILHORAT, Am. J. Psychiat. **100**:681 (March) 1944.

Small and Milhorat studied 4 cases of anorexia nervosa, investigating the psychopathologic reactions and their relation to the organic changes and the alterations of somatic functions concerned with metabolism. In all 4 cases there was refusal to eat due to aversion or fear of food. The appetite was not impaired. No specific dynamic factors could be elicited, and frank compulsvie features were absent. Restless overactivity

was marked and was dependent on anxiety. In treatment of the problem the symptoms were disregarded, and attention was directed to the anxiety. Food intake, urinary and fecal output, basal metabolic rate and nitrogen and creatinine excretion in the urine were studied. The authors conclude that there is no basis for postulating a primary metabolic disorder.

FORSTER, Philadelphia.

SCHIZOPHRENIA IN A FOUR YEAR OLD BOY. H. ROBERT BLANK, OLIVE CUSHING SMITH and HILDE BRUCH, Am. J. Psychiat. **100**:805 (May) 1944.

Blank, Smith and Bruch report studies on a 4 year old boy with schizophrenia. The family history revealed an extensive psychopathic trend. The home atmosphere was crowded with fears and terrors, and the mother was almost as sick as the patient. The early development was normal, but there was a gradual development of seclusiveness, terrors, apathy and temper tantrums. Examination revealed that the patient was aloof, preoccupied and self absorbed, while productivity was sparse. In observed play there was more urgency, and laughter became increasingly shrieking and excited. During the course of nine months' study in group situations, the patient was found to be passive, dependent and seclusive; the productions showed echolalia and jargon manifestations, and contact was transitory. Early in the course of therapy some catatonic features and faulty toilet habits were present. On retiring, he babbled incoherently for long periods and had night terrors. At the time of discharge a happy adjustment had been made at a simple level, but the child remained a withdrawn, blocked and passive personality.

The authors evaluate the familial interpersonal relationships in this case and conclude that the child's symptoms might be considered as defensive stratagems yielding him protection from a threatening world.

FORSTER, Philadelphia.

CHEMOTHERAPEUTIC PROPHYLAXIS WITH SULFONAMIDE DRUGS: II. THE EFFECT OF SMALL DOSES OF SULFATHIAZOLE OR SULFADIAZINE ON MENTAL EFFICIENCY AND HAND-EYE COORDINATION. F. W. REYNOLDS and G. W. SHAFFER, Am. J. Syph., Gonor. & Ven. Dis. **27**:563 (Sept.) 1943.

Reynolds and Shaffer point out that the widespread use of small doses of sulfonamide drugs as chemotherapeutic agents for the prevention of venereal infections (gonorrhea, chancroid and lymphogranuloma venereum), especially by the armed forces, makes desirable some information as to the effect of these drugs on the physiologic and psychologic processes on which fighting efficiency depends. A study was undertaken to determine what effects sulfathiazole and sulfadiazine have on mental efficiency and on hand to eye coordination. Two groups of subjects were used for this study: (1) a group of 24 army medical officers and (2) a group of 49 university senior students. In each group, preliminary examinations were made in order to establish a base line. Sulfathiazole or sulfadiazine was administered in divided doses over a twenty-four hour period, and the same tests were repeated six hours and (in group 2 only) thirty hours after the last dose of the drug had been given. Half of the subjects in group 1 received a total of 6 Gm. of sulfathiazole each, the other half receiving inert placebos similar in appearance to sulfathiazole tablets. In group 2 each of 19 subjects received 4 Gm. of sulfathiazole; 20 subjects received 4 Gm. of sulfadiazine, and 10 subjects were given inert placebos. Comparison of the sulfonamide-treated groups with the controls reveals no statistically valid change in mental efficiency or hand to eye coordination following either drug. A few subjects receiving sulfathiazole appeared to have an idiosyncrasy to the drug, since their performance was notably below that of all others. None of the subjects given sulfadiazine showed such an idiosyncrasy.

J. A. M. A.

"SHOCK" THERAPIES. GEORGE ALEXANDER, J. Nerv. & Ment. Dis. **99**:922 (June) 1944.

Alexander points out that in evaluation of the results of shock therapies there has been failure to consider the time factor properly, so that in some instances improvement occurring two or three months after the cessation of treatment has been attributed to the shock therapy. This tendency disregards the natural trend toward spontaneous improvement of many psychiatric conditions. The author suggests that in any case in which there was not sufficient improvement to allow the patient to leave the hospital within thirty days of the termination of his treatment the therapy be considered to have failed.

CHODOFF, Langley Field, Va.

PROBLEMS OF NAVAL PSYCHIATRY. FRANCIS J. BRACELAND and HOWARD P. ROME, War Med. **6**:217 (Oct.) 1944.

Braceland and Rome point out that unfitness for the armed services does not mean that the so-called unfit man is a maladjusted person in the civilian sense. In the armed services a man must adjust completely or he is unfit, and it is the psychiatrist who initiates his discharge. This causes him to be classified as a psychiatric casualty and raises the mistaken impression that because hundreds of thousands of such discharges are made this is a nation of misfits. What this really amounts to is that training, specialization, and singleness of purpose in education have made the national quality of adjustment a little too brittle. War brings all emotional and characterologic defects into the foreground because of the tension and pressure under which the group labors. These blemishes are serious from a military standpoint, but they are not disabling on the well cared for face of civilian life.

The psychoses which occur early in the recruit's career, or even later in shore installations, do not differ from those seen in civilian life. One of the few new syndromes has been called "three day schizophrenia." It is an acute fulminant state in which the mental content is indistinguishable from schizophrenia but more confusion and more frequent visual and auditory hallucinations are present. It develops in a previously well adjusted personality and subsides completely in three to five days. It arises in response to environmental stress—overexertion, long periods of sleeplessness, loss of weight and intense activity under trying conditions. Rest and sedation bring about miraculous changes in short periods.

An interesting and noteworthy fact in this war is the rapid and high recovery rate of psychotic patients. Acute psychotic casualties during combat are rare among Naval personnel afloat. Symptoms of emotional distress are common but are not per se a cause for hospitalization. The Navy has designated the symptom complex of heightened irritability, symptoms referable to the autonomic nervous system, fatigue and personality changes occurring after severe combat in a previously emotionally sound person as "combat fatigue." This diagnosis in the Navy is used only as a working basis, and no one is ever discharged with this label.

In this war hysteria is not reported as often as in World War I, and there seem to be more instances of gastrointestinal disturbances and fewer of disordered action of the heart.

Emphasis is on group therapy of a short, active nature, using every possible aid, and recovery is judged in terms of effectiveness rather than of insistence on complete insight.

PEARSON, Philadelphia.

ETIOLOGY AND PATHOGENESIS OF NEUROCIRCULATORY ASTHENIA: I. HYPERTHERMIA AS ONE OF THE MANIFESTATIONS OF NEUROCIRCULATORY ASTHENIA. MEYER FRIEDMAN, War Med. **6**:221 (Oct.) 1944.

Approximately 36 per cent of a series of patients with a condition diagnosed as neurocirculatory asthenia were found to have an episodic type of fever, accompanied with moderate tachycardia, increased tremor, localized perspiration and coldness of the skin of the extremities.

Despite extensive clinical, laboratory and roentgenographic investigations, no evidence of infection was found in any of the hyperthermic patients. The character of the fever was found to differ in certain respects from that of fever observed in patients with a typical chronic infectious process. The hyperthermic patients also exhibited during their febrile periods significantly different clinical conditions than those usually found in febrile patients suffering from chronic infectious disease.

Epinephrine hydrochloride, amphetamine sulfate, citrated caffeine, typhoid vaccine and psychic stimuli were found capable of inducing elevations of temperature in these patients during normally afebrile periods. No sedative, however, was found which was capable of preventing or reducing their febrile reactions.

The fever, with its accompanying signs, observed in these patients is thought to result from abnormal activity of the hypothalamus.

PEARSON, Philadelphia.

## Meninges and Blood Vessels

PRIMARY SYPHILIS TREATED BY TWENTY-SIX WEEK COURSE OF MAPHARSEN AND BISMUTH: ACUTE BASILAR MENINGITIS WITH NEURORETINITIS DEVELOPING DURING TREATMENT. GERARD A. DE OREO, Arch. Dermat. & Syph. **49**:109 (Feb.) 1944.

De Oreo reports the case of a patient who had weakly seropositive primary syphilis for which he had received combined therapy. In the thirtieth week of treatment, after a total of forty injections of oxophenarsine hydrochloride (2,400 mg.) and twenty-two injections of bismuth subsalicylate, severe occipital headache developed, followed by a state of excitement, in which he was confused, argumentative, irrational and disoriented. Neurologic examination showed paresis of the left and right abducens nerves. Examination of the fundi revealed bilateral papilledema of 3 to 4 D., the optic disks were indistinct and covered with an exudate and flame-shaped hemorrhages. Visual acuity was impaired. The patient also exhibited moderate stiffness of the neck. The remainder of the neurologic examination revealed nothing unusual except for a slight tremor and some hesitation in the performance of the tests of coordination. The Kahn reaction of the blood was negative. Examinations of the cerebrospinal fluid on two successive days revealed cell counts of 441 and 434 cells per cubic millimeter, with 7 per cent polymorphonuclear leukocytes and the remainder lymphocytes. The Pandy reaction was strongly positive, and the colloidal gold curve was 4455431221. The Wassermann reaction of the spinal fluid was positive with 0.1, 0.25 and 0.5 cc. and anticomplementary with 1 cc. The diagnosis was acute syphilitic basilar meningitis with neuroretinitis.

The patient's symptoms and abnormal signs disappeared after a course of ten treatments and thirteen injections of neoarsphenamine and five injections of bismuth subsalicylate. The cerebrospinal fluid revealed only 7 cells per cubic millimeter, with a trace of globulin and an almost normal colloidal gold curve. The Wassermann reaction of the spinal fluid showed a slight decrease in titer.

The author states: "Perhaps the one warning note was the low titer of the serologic reactions early in the disease and the speed with which it began to decrease, with complete reversal in three months. In the light of the unfortunate relapse, the serologic reactions must be interpreted as a result of poor immunologic response rather than of prompt therapeutic effect. The persistently negative Kahn reaction and the only temporary relapse of the Wassermann reaction in the face of an almost overwhelming meningeal involvement may be further expression of a lack of immunity. Fever cabinet therapy combined with administration of neoarsphenamine has resulted in clinical recovery and satisfactory improvement of the condition of the spinal fluid."

GUTTMAN, Philadelphia.

BINOCULAR PAPILLEDEMA IN A CASE OF TORULOSIS ASSOCIATED WITH HODGKIN'S DISEASE. MARTIN COHEN, Arch. Ophth. **32**:477 (Dec.) 1944.

Cohen reports a case in which torulas were demonstrated in the brain tissue, as well as in the secretions covering the cortex of the cerebrum and the pons, with production of leptomeningitis at the base of the brain. Edema of the brain was present, with dilatation of the ventricles. The aqueduct of Sylvius was partially occluded by exudate. These pathologic changes were the result of the torular infection. The unusual feature in the case was pronounced binocular papilledema due to Hodgkin's disease.

SPAETH, Philadelphia.

CONGENITAL ARTERIAL ANEURYSM AT THE PAPILLA. FREDERICK H. THEODORE and WILLIAM H. BONSER, Arch. Ophth. **32**:492 (Dec.) 1944.

The anatomy of the optic papilla is so important that any deviations from the normal must be seriously considered. There is considerable confusion in the classification of aneurysms of the retinal vessels, and it is convenient to divide the lesions in the various cases thus far reported into three types: (1) aneurysms of the larger branches of the central retinal artery, all of which appear to have occurred secondary to vascular disease or trauma, and which are generally associated with visual impairment; (2) miliary aneurysms, which are of two types, one essentially a senile degenerative phenomenon and the other neoplastic, and (3) arteriovenous aneurysms, which are essentially congenital in origin and are often without associated visual disturbances. The third category is of additional interest in that recent articles have called attention to the association of this striking anomaly with similar arteriovenous aneurysms in the skin and brain. The aneurysm in the case reported corresponded to none of these types but resembled the third in several important details, although the aneurysm was entirely arterial.

SPAETH, Philadelphia.

ENINGOCOCCIC MENINGITIS. E. B. MEWBORNE, I. S. TOLPIN and G. HIRSCHBERG, Virginia M. Monthly **70**:492 (Oct.) 1943.

Mewborne and his associates report 27 cases of epidemic meningitis at the Riverside Hospital, Newport News, Va., during a six month period. During increased prevalence of epidemic meningitis spinal puncture should become a routine measure. In all questionable cases repeated punctures should be done at twenty-four hour intervals. It is essential to watch for cases of the atypical form, such as the severe septicemic form. Absence of signs of meningeal irritation does not exclude meningitis. The authors cite 3 cases in which stiff neck and Kernig's sign were absent. Three cases are reported because of the rapidity of onset; there was little or no prodromal period. In 1 case meningococcic pneumonia developed, which did not respond to treatment. Age plays a decisive part in prognosis; in children and young persons the outlook is favorable. The average case of epidemic meningitis will respond to adequate sulfadiazine therapy in from twenty-four to forty-eight hours. Treatment should be aimed at the early procurement of a high sulfadiazine level in the blood by a high initial dose followed by an adequate maintenance dose. Renal complications due to toxicity produced by the drug can be averted or mitigated by (*a*) alkalinization and forcing of fluids, (*b*) daily urinalysis and charting of the intake and output of fluids and (*c*) discontinuance of sulfadiazine when signs of renal lesions develop.

J. A. M. A.

## Diseases of the Brain

AFTER-IMAGE PERIMETRY: A RAPID METHOD OF OBTAINING VISUAL FIELDS; PRELIMINARY REPORT. W. P. WILLIAMSON, Arch. Ophth. **33**:40 (Jan.) 1945.

The instrument which Williamson used utilizes the positive and negative after-images as the patient projects them on a translucent cover, as a design of white lines is projected on a black background. After studying the positive and negative after-images for two minutes, the patient is able to chart his own visual field, thus outlining any areas not visualized in the after-image.

The phenomenon of after-image has long been known and studied, but it has apparently not been used as a means of perimetric determination. It is reasonable to suppose that if an after-image were produced in a patient with a lesion of the central optic pathways there might be a defect in the after-image corresponding to the site and size of the area of damage of the visual system.

According to the author, the advantages of this method of obtaining visual fields are as follows: 1. The method is not tiring to the patient or to the examiner. 2. The patient is unable to look away from the fixation point, since the after-image moves simultaneously with any shift of the eye. 3. With a hand lamp the method is readily adaptable to the bed patient, who sees the after-images on the ceiling. 4. With a simple design of an object in each quadrant, the method can be used for children, who find the phenomenon attractive. 5. Fields can be conveniently determined daily for patients with tumor of the pituitary gland who are receiving roentgen ray therapy, for patients with active multiple sclerosis with changing scotomas or for patients with any type of abnormal visual fields undergoing rapid change. 6. The method is time saving, enabling one technician to increase the number of fields charted from seven to seventy or more a day. 7. It is readily adapted to the physician's office. 8. It can be used in processing methods, such as routine examinations for the armed services. 9. The apparatus is simple and easily available, since it consists only of a flood lamp and a cloth shield, which any seamstress can prepare overnight.

The disadvantages are as follows: 1. The normal blindspot is not visualized, since it has no cortical representation. An enlarged blindspot, however, can be visualized in the after-image. 2. It will no doubt prove to be less accurate than the tangent screen method, though thus far it appears to be accurate enough for clinical use. This can be determined only after further study. 3. With the present technic the portion of the peripheral field tested does not represent more than 45 degrees. 4. The method reveals only absolute field defects.

SPAETH, Philadelphia.

CYSTIC HYDROPS OF THE PINEAL GLAND. JESSE L. CARR, J. Nerv. & Ment. Dis. **99**:552 (May) 1944.

Cysts of the pineal gland are of three types: (1) small single or multiple cavities, which cause no enlargement of the gland and are present in 38 per cent of pineal bodies examined; (2) cysts associated with pineal tumor, particularly teratoma and pinealoma, and (3) cysts not associated with tumor, usually single and large enough to distend the gland and to cause pressure symptoms.

Carr reviews the literature on the last type, which is called hydrops cysticus glandulae pinealis. Of the theories of the origin of pineal cysts, that of glial degeneration due to ischemia is the most widely held. The clinical picture of cystic disease of the pineal gland consists of a combination of neurologic and endocrine signs. Although precocious senility has been reported, macrogenitosomia has not been attributed unequivocally to a non-neoplastic pineal cyst.

The author reports the clinical and autopsy records of 6 cases of cystic hydrops of the pineal gland. In 2 cases the patient suffered from a depressive psychosis, ending in each instance in a sudden decision to commit suicide. This points to a possible relation between mental disease and cystic hydrops of the pineal gland. In 3 cases there was sudden death. The possibility that precocious senility may be associated with degeneration of the pineal parenchyma is illustrated in a case in which extraordinarily sclerotic arteries about the thyroid were noted. In half the cases some degree of internal hydrocephalus due to compression of the iter was present. The contents of the cysts varied from clear fluid to amorphous debris. In none of the cases was a clinical diagnosis of cystic hydrops of the pineal gland made or suspected.

CHODOFF, Langley Field, Va.

BULIMIA ASSOCIATED WITH EPILEPSY IN CHILDREN. B. VIJNOVSKY, Rev. argent. de neurol. y psiquiat. **9**:344 (Sept.) 1944.

Vijnovsky reports 18 cases of bulimia among 66 epileptic children. The symptom had been present since birth in 10 cases, appeared simultaneously with the attacks in 4 cases, five years before the onset of attacks in 1 case and nine years after the onset of attacks in another case. In 1 case the bulimia was accompanied by polydipsia; in another an episode of intense hunger was the prodrome of an epileptic attack. In 4 cases the bulimia disappeared simultaneously with the disappearance of the attack. No increase in weight was observed in spite of the excessive intake of food. In 9

cases blood sugar levels were determined, and they were all normal (80 to 110 mg. per hundred cubic centimeters). In 2 cases pica was present. The author believes that the increase in appetite is due to an epileptogenous focus in the frontal lobe which, at the same time, inhibits lower, probably hypothalamic, centers controlling appetite.

SAVITSKY, New York.

ACUTE MULTIPLE SCLEROSIS. ALUIZIO MARQUES, Rev. neurol. de Buenos Aires **8**:271 (July-Sept.) 1943.

Since Babinski called attention to the acute form of multiple sclerosis, in 1885, there has been a considerable difference of opinion as to the relation of this form of multiple sclerosis to disseminated encephalomyelitis. The author believes these two conditions are distinct clinically, although histopathologically they cannot be differentiated. The acute form of multiple sclerosis rarely lasts more than a year; muscle atrophy is commoner than in the chronic form; there is more frequent involvement of the brain stem, especially the bulb, and mental changes are more common. McAlpine called attention to the following important differences between multiple sclerosis and acute disseminated encephalomyelitis: 1. The presence of a febrile reaction is in favor of encephalomyelitis. 2. Pain is rarer in multiple sclerosis than in the infectious disease. 3. Euphoria is rare in cases of encephalomyelitis. 4. One seldom encounters depressed reflexes in cases of multiple sclerosis. The author reports 1 case each of acute multiple sclerosis and encephalomyelitis disseminata. Not more than 50 verified cases of acute multiple sclerosis were found in the literature.

In the first case, a woman aged 35 had an illness of five months, ending in death. During convalescence from malaria, she began to complain of weakness in the lower limbs and of diminution of vision in the right eye. She was hospitalized two months after the onset of the disorder. Neurologic examination soon after her admission to the hospital showed scanning speech, horizontal nystagmus, cerebellar signs in all extremities, absence of abdominal reflexes, exaggerated knee and ankle jerks and positive Babinski, Rossolimo and Mendel-Bechterew signs; there was decided diminution of vision with optic nerve atrophy bilaterally. Examination of the spinal fluid revealed nothing abnormal. There was a rather pronounced remission for about three weeks, followed by complete amaurosis, confusion, incontinence, marked cerebellar signs and spasticity in the lower limbs. Soon afterward there was flaccid quadriplegia, with absence of all reflexes, both deep and superficial. Just before her death there was evidence of involvement of the medulla.

Autopsy showed many patches of demyelination and necrosis, especially in the periventricular and subependymal regions. Myelin sheaths and axis-cylinders were destroyed; little glial proliferation had occurred within the zone of necrosis. There was a considerable amount of cellular infiltration, chiefly lymphocytic and perivascular, and numerous compound granular cells were noted. Around the lesions was intense proliferation of protoplasmic astrocytes. The lesions were more accentuated in the posterior part of the lateral ventricles. There were numerous foci of cellular infiltration, especially in the medulla. Similar areas of degeneration were noted in the cervical portions of the posterior columns.

In the second case an 18 year old white Brazilian youth had sudden onset of the disease four days prior to admission, with choking sensations, which were soon followed by paresthesias in the upper and then in the lower limbs. After a few hours the lower limbs became paralyzed, and soon afterward the upper limbs were involved. Paralysis of the right arm cleared up the next day. The patient was unable to urinate spontaneously. Neurologic examination showed flaccid paraplegia, with absence of superficial and deep reflexes; there were no ocular lesions and no mental changes; the left arm was paralyzed. The patient had to be catheterized. Bed sores appeared and became infected but improved later. The patient continued to be gravely ill for about six months. The case was considered to be one of acute encephalomyelitis.

SAVITSKY, New York.

## Diseases of the Spinal Cord

EFFECT OF ACTIVATED SLUDGE PROCESS OF SEWAGE TREATMENT ON POLIOMYELITIS VIRUS. H. J. CARLSON, G. M. RIDENOUR and C. F. MCKHANN, JR., Am. J. Pub. Health **33**:1083 (Sept.) 1943.

Carlson and his associates investigated the effect of the activated sludge process as used in municipal sewage disposal plants on the removal or inactivation of a mouse-adapted strain of poliomyelitis virus. Virus suspension 1:300 was used in sludge concentrations of 1,100, 2,200 and 3,300 parts per million with aeration periods of zero, six and nine hours. The results indicate that activated sludge in amounts as low as 1,100 parts per million with six hours' aeration will remove or inactivate the virus to a sufficient extent to reduce greatly infectivity for mice given intracerebral injections. Heavier concentrations of sludge with longer aeration periods largely eliminate infectivity.

J. A. M. A.

RECENT ADVANCES IN TREATMENT OF RUPTURED (LUMBAR) INTERVERTEBRAL DISKS. W. E. DANDY, J. M. A. Alabama **13**:129 (Oct.) 1943.

According to Dandy, spontaneous cures in cases of ruptured intervertebral disk are rare, although temporary remissions are the rule. There are two components of a ruptured disk: (1) the necrotic interior causing backache, and (2) the protruding portion, causing sciatica. The diagnosis of a ruptured disk is made solely from the signs, symptoms and roentgenographic results of examination of the spine. Spinal injections of contrast medium and spinal punctures are contraindicated; they are unnecessary, and they will lead to the diagnosis of only one third of the total number. The small (concealed) disks outnumber the protruding ones 2 to 1. They cannot be detected with spinal injections of contrast mediums. Two disks are involved in about 80 per cent of cases, and occasionally there is a third ruptured disk. The exposure is unilateral and between the laminas without removal of bone (Love's operation), or, when the interlaminal opening is too small, the removal of a small bite of lamina may be necessary. Mobility of the vertebra, tested by pressure on the spinous process, will usually determine whether the disk is the fourth or the fifth lumbar (98 per cent are at these two disks) or both. The entire necrotic content of the interior of the disk should be thoroughly removed with curets. This is the best insurance against recurrences. Fusion operations are unnecessary and are contraindicated. Fusion of the vertebrae occurs after removal of the necrotic contents of the disk. The reason for the localization of 98 per cent of the rup-

tured lumbar disks to the fourth and fifth is probably a shift in the plane of the lateral articular processes from the horizontal to a transverse direction.

J. A. M. A.

ATTEMPTS TO RECOVER POLIOMYELITIS VIRUS FROM FRUIT, WELL WATER, CHICKEN CORDS AND DOG STOOLS. J. A. TOOMEY, W. S. TAKACS and L. A. TISCHER, J. Pediat. **23**:168 (Aug.) 1943.

Toomey and his associates made attempts to recover the virus of poliomyelitis from fruit (washings), well water, stools from sick dogs and cords of paralyzed chickens found in vicinities where cases of human poliomyelitis had occurred. Although the virus may have been present in the specimens tested, its existence could not be demonstrated when either the eastern cotton rat or the Macaca mulatta monkey was used as the test animal.

J. A. M. A.

ASPECTS OF TABES DORSALIS. CARLOS LAMBRUSCHINI, Rev. argent. de neurol. y psiquiat. **9**:281 (Sept.) 1944.

Lambruschini reports 22 personally observed cases of tabes dorsalis, with emphasis on neuroarthropathies encountered with this disease. In 2 cases polyarthropathies were present; in 1 a knee, a hip joint and the lumbar portion of the spine were involved, and in the other a hip and the spine were affected. There were 3 cases in which only one joint was involved. The author comments on the absence of optic nerve atrophy in cases of arthropathy, though he admits that his number of cases is insufficient to warrant a definite statement about this correlation. In 1 of the cases there was a question about the etiologic role of trauma to the joint. He does not believe that injury is significant in accounting for the localization of the changes in the joint. In 2 of the cases there was significant anemia. He attributes this anemia to the syphilitic process.

SAVITSKY, New York.

## Peripheral and Cranial Nerves

PARALYSIS OF THE LARYNX: AN EARLY SIGN OF RECURRENCE FOLLOWING RADICAL MASTECTOMY FOR CARCINOMA. J. R. FOX, Arch. Surg. **49**:388 (Dec.) 1944.

Hoarseness occurring after radical mastectomy for carcinoma of the breast is often the first clinical evidence of metastasis. Metastasis from carcinoma of the breast causes paralysis of the recurrent laryngeal nerve on the same or on the opposite side by involving the chain of lymph nodes surrounding the recurrent laryngeal nerve. Six illustrative cases are reported.

LIST, Ann Arbor, Mich.

## Vegetative and Endocrine Systems

THE EFFECT OF ADRENALECTOMY UPON THE BRAIN OF WHITE RATS. ARTHUR WEIL and RICHARD A. GROAT, J. Neuropath. & Exper. Neurol. **3**:374 (Oct.) 1944.

Weil and Groat performed adrenalectomies on 2 rats 57 days old and killed them seventy-five days after operation.

The observations indicate that adrenalectomy in male and female rats is followed by an increase in the weight of the brain. This is due to an increase in water and in other compounds, such as neutral fats, fatty acids, cholesterol and its esters, without any notable change in the qualitative composition of the brain and the proportional distribution of the different compounds. In the male rat the testes and prostate gland are increased in weight. In both sexes the heart and thyroid increase in weight without any change in the hypophysis.

GUTTMAN, Philadelphia.

PEPTIC ULCER IN THE CANADIAN ARMY (1940 TO 1944). W. R. FEASBY, War Med. **6**:300 (Nov.) 1944.

Feasby found that only 10 per cent of a selected group of men with healed duodenal ulcer were able to carry on indefinitely after return to duty, either in England or in Canada. In induction examinations there is an error of about 12 per cent in the diagnosis of duodenal ulcer.

PEARSON, Philadelphia.

## Treatment, Neurosurgery

STUDIES ON 2-SULFAMIDO-4-METHYL-PYRIMIDINE (SULFAMERAZINE, SULFAMETHYLDIAZINE) IN MAN: III. TREATMENT OF MENINGOCOCCIC MENINGITIS, W. I. GEFTER and others, Am. J. M. Sc. **206**:211 (Aug.) 1943.

Sulfamerazine is one of several methyl homologues of sulfadiazine. Gefter and his associates used sulfamerazine for meningococcic meningitis during an epidemic of that disease in Philadelphia in the winter of 1942-1943. They report observations on 45 patients. The initial dose was always given intravenously as sulfamerazine sodium (5 per cent solution in sterile distilled water), adults receiving 3 Gm. and children 1 to 2 Gm. This dose was immediately followed by oral administration of the drug, adults receiving 1 Gm. every four hours and children 0.25 to 1 Gm. every six hours. Delirious or comatose patients were given the drug by nasal tube until they were capable of taking medication by mouth. Sulfamerazine was continued until the patient appeared entirely well clinically. In the successfully treated group the average total dose of the drug for adults was 56.4 Gm., given over an average period of nine and a half days; the children received an average total dose of 19.3 Gm., over an average period of eight and six-tenths days. Five of the patients were given antimeningococcus serum intravenously, in addition to sulfamerazine. Determinations of the amount of free drug in the blood were made at frequent intervals. Three deaths occurred in this series, a mortality of 6.7 per cent. This is to be compared with the 57.5 per cent mortality occurring in 40 cases of this disease at the Philadelphia General Hospital during 1935, 1936 and 1937, and with the 40 per cent of 50 cases reported in 1942. The results also compare favorably with those in which sulfadiazine was employed (12.5 per cent mortality). Clinical improvement, with return of mental clarity, occurred in 70 per cent of the patients within forty-eight hours. The average time observed for the return to normal temperature was five and two-tenths days. Toxic reactions attributable to sulfamerazine, occurring in each instance after the fifth day of treatment, were noted in 11 patients.

J. A. M. A.

CRANIOCEREBRAL WOUNDS: EXTERIORIZATION METHOD OF TREATMENT. J. BROWDER, Am. J. Surg. **62**:3 (Oct.) 1943.

Browder for several years has been applying a method for treatment of neglected wounds of the brain

which is patterned after the plan of exteriorization of cerebral abscess as recommended by King. This method prevents the formation of fungus cerebri. The scalp, bone, dura and brain are debrided, and all softened cerebral tissue is removed by suction, hemostasis being secured by applying the electrocoagulating current to the metal tube of the sucker whenever a blood vessel is drawn into it. The dura should be cut away to the limits of the cerebral defect. After débridement, cerebrospinal fluid should be withdrawn through the spinal needle in order to reduce the possibility of cerebral herniation. After the cerebral cavity has been opened widely, the entire area is covered with a single layer handkerchief of mesh gauze (44 by 40 per square inch). Sulfanilamide crystals are blown on to the handkerchief lining the cavity. The cavity is then packed with ½ inch gauze strips to the level of the scalp. The flaps of scalp are brought over the area and loosely approximated. A snug-fitting dressing composed of wet, flat gauze, held firmly in place by a skull cap, should be applied to prevent herniation. The wound is not dressed for three to five days. For dressing the patient is placed on his side, cerebrospinal fluid is withdrawn from the lumbar thecal sac, the wound is reopened and the gauze pack is removed. The cavity lined with the adherent gauze handkerchief is filled with full strength hydrogen peroxide and washed out with saline solution. This should be repeated three or four times before an attempt is made to loosen the handkerchief. The removal of the lining gauze at the first dressing is a slow and tedious procedure, but each dressing becomes less arduous. In about ten to twelve days the entire cavity is covered with granulation tissue, the surface of which must not be injured during dressings. Slowly the cerebral wound becomes smaller, and finally, by gradual decrease in the amount of intracranial packing, the granulating surface rises to the level of the cranial vault. After epithelization becomes complete, plastic repair of the scalp and cranial defect may be carried out.

J. A. M. A.

GENERAL SANARELLI-SHWARTZMAN PHENOMENON WITH FATAL OUTCOME FOLLOWING TYPHOID VACCINE THERAPY. ERICH URBACH, HAROLD L. GOLDBURGH and PHILIP M. GOTTLIEB, Ann. Int. Med. **20**:989 (June) 1944.

Urbach, Goldburgh and Gottlieb report the case of a woman aged 40 who was treated for "infectious arthritis" with triple typhoid vaccine. After the third treatment (10,000,000 organisms given by the intramuscular route and 75,000,000 injected intravenously) the patient experienced a severe chill, and within two hours the temperature rose to 99.6 F. and then dropped precipitously to 96.4 F. The patient went into peripheral vascular collapse and died six and one-half hours after the injection. Necropsy revealed widespread cutaneous and visceral petechial hemorrhages; lack of coagulation of the blood, and intense congestion of the lungs, intestines and muscles, associated with necrosis of the kidneys, liver and adrenal glands. These observations correspond to the changes associated with the general Sanarelli-Shwartzman phenomenon in experimental animals.

GUTTMAN, Philadelphia.

THE TREATMENT OF RHINORRHEA AND OTORRHEA. W. E. DANDY, Arch. Surg. **49**:75 (Aug.) 1944.

Cerebrospinal fluid rhinorrhea and otorrhea result from abnormal fistulous openings between the subarachnoid or ventricular spaces and the accessory paranasal sinuses or mastoid air cells. These conditions are most frequently caused by fracture of the skull or an opening created by operation; they are rarely due to erosion produced by tumor or infection or to a congenital defect.

The escape of cerebrospinal fluid may cease spontaneously, as it does in cases of otorrhea following fracture of the petrous bone. Leakage persisting longer than two weeks must be treated surgically, since sooner or later meningitis or brain abscess will develop. While the operation is practically free from danger, death may follow the closure of the fistula if an intracranial infection has already been present.

The fistula may be closed in the following ways: (1) direct suture of the dural opening; (2) dural closure by free fascial transplant; (3) closure of the bony opening by a flap of dura or other soft tissue; (4) sealing of the bony opening with wax.

Dandy reports 11 clinical cases; 8 of the patients were cured permanently by surgical intervention; 2 died of intracranial infection, and in 1 patient the leakage of spinal fluid persisted because the fistula was not found at operation.

As a rule, the location of the fistula can be determined by the site of the causative fracture or operative defect in the skull; in rare instances, however, it may be impossible to find the opening. In 1 observation a fistula could be demonstrated by injection of methylthionine chloride (methylene blue).

Spontaneous pneumocephalus and porencephaly may develop as a result of a ball valve mechanism but may disappear after closure of the fistula.

A fistula through the frontal sinus caused by a depressed fracture is treated by elevating the depressed fragments of bone, suturing or covering the dural defect with fascia and then replacing the fragments of bone. If no depressed fracture is present, rhinorrhea is best treated by formation of a unilateral frontal bone flap on the side of the leakage. If the fistula is not found, a similar operation may have to be performed on the other side; at any rate, two small osteoplastic flaps are preferable to a single large bilateral exposure.

Cerebrospinal rhinorrhea does not always indicate that the fistula originates from the ethmoid or the frontal sinus; it may develop from an opening in the mastoid which drains through the middle ear and the eustachian tube.

LIST, Ann Arbor, Mich.

DIETHYLSTILBESTROL IN THE MANAGEMENT OF PSYCHOPATHOLOGICAL STATES IN MALES. R. M. FOOTE, J. Nerv. & Ment. Dis. **99**:928 (June) 1944.

In the cases selected for this study, it was felt that psychosexual conflicts were present as the result of excessive sexual drives. With the idea that gonadal function was responsible and that its partial suppression would effect dissolution of the conflict, diethylstilbestrol was employed for its secondary effect of inhibiting production of androgen. The diethylstilbestrol was given in daily doses of 1 or 2 mg. One case is reported, that of a 19 year old youth who masturbated four or five times a day and displayed intense sexual preoccupations. With diethylstilbestrol therapy there were notable lessening of the sexual drive and improvement in the general personality and behavior. After thirty-two days without treatment his original state returned, but with resumption of diethylstilbestrol therapy improvement again appeared. Encouraging results have been obtained with the use of this therapy in other cases.

CHODOFF, Langley Field, Va.

ARTIFICIALLY INDUCED FEVER AS A THERAPEUTIC PROCEDURE. W. R. CARSON, Psychiatric Quart. **17**:604 (Oct.) 1943.

Carson describes the results of artificial fever treatment of patients in mental hospitals over a period of eleven years. Of 122 patients with dementia paralytica, there was some improvement in 67 per cent; of 17 patients with cerebral syphilis there was some improvement in 76 per cent; all 5 patients with tabes showed improvement. Patients with acute, sulfonamide-fast gonorrhea responded fairly well to fever therapy. Two deaths among patients with dementia paralytica were definitely associated with treatment.

Patients with pulmonary tuberculosis and dementia paralytica were treated with fever, without any harm to the pulmonary condition. Patients with dementia paralytica who suffered from convulsions were also given fever therapy, with administration of phenobarbital before and during treatment. This method met with no complications. The author does not regard either of these conditions as contraindications to fever therapy in a patient with dementia paralytica, since most untreated patients die in two years or so.

This series of patients were given artificial fever therapy at first by means of general diathermy or use of a sleeping bag and the inductorium. In the past six years the inductorium plus a cabinet with humidified air was used. Treatment was usually given only once a week, for five hours at a time (three hours at a temperature of over 103.6 F. and two hours at a temperature of 106 F. or over). A minimum total of seventy hours "offers the maximum chance of improvement." But the author has "tried not to stop any treatment while a patient is still improving."

Carson feels that the results compare at least equally well with malarial therapy and that therefore artificial therapy is the method of choice, since it "obviates the necessity of introducing another disease into the body; is easy to control; treatment can be given on an individual basis and prolonged, if necessary; and many patients who could not stand malaria are able to take artificial fever without difficulty." However, he points out that too much emphasis cannot be placed on careful supervision during treatment.

He calls special attention to the unanimity of all reports on treatment of dementia paralytica in emphasizing that the earlier such help is given the better the chances for remission.

McCARTER, Philadelphia.

NEUROSURGERY AND RADIATION FOR RELIEF OF PAIN IN ADVANCED CANCER. GEORGE COOPER JR. and VINCENT W. ARCHER, Radiology **42**:142 (Aug.) 1944.

Cooper and Archer report 3 cases of advanced malignant growths: an angioendothelioma of the spermatic cord, a carcinoma of the breast and a Ewing sarcoma of a rib. Through persistent and repeated roentgen ray treatment of the metastases, each patient enjoyed a remarkable period of survival, in fairly good health. The case of the Ewing sarcoma was most remarkable. The 6 year old victim, with many pulmonary metastases, recovered from a moribund state after roentgen ray treatment. Thirteen years later she was in perfect health, and the roentgenogram of the chest showed a completely normal condition.

Emphasis is placed on the early roentgen ray treatment for localized pain in patients known to have a malignant growth. Even though no metastases are demonstrable, both the suffering and the chance for pathologic fracture are decreased.

Three other cases of hopeless malignant neoplasm are described, in which neither radiation nor opiates could control the pain. Peripheral nerve injection, posterior root resection and chordotomy respectively produced complete relief from pain for the remaining few months of life.

"When considering the advisability of neurosurgery, the possibility of unpleasant results must be weighed. Loss of sensation, loss of sphincter control, and paralysis are ever present dangers, and the pain should be more difficult to live with than the possible complications before they are risked."

TEPLICK, Washington, D. C.

## Diseases of the Brain

MYASTHENIC SYNDROME OCCURRING WITH MALARIA. MARIO MENDEZ and MANUEL CHAVEZ, Rev. de neuro-psiquiat. **7**:335 (Sept.) 1944.

Mendez and Chavez stated that they know of no reported case in which a myasthenic syndrome occurred during malaria. They report the case of a boy of 7½ years who sustained a mild head injury toward the end of December 1943. The next day fever developed. He had a few rises in temperature on alternate days, which subsided spontaneously without specific treatment. After the last day of fever, ptosis of the left eyelid appeared and was followed a day later by diplopia. Soon afterward, ptosis appeared on the right side, associated with difficulty in mastication. One week after appearance of the ptosis, the patient had marked dysarthria for twenty-four hours. All the complaints were intensified by fatigue and were more severe toward evening. Later, bilateral ptosis developed, as well as paralysis of the right external rectus muscle, associated with elevations of temperature on alternate days. The patient was admitted to the hospital and soon afterward had two febrile episodes, on succeeding days. Malarial organisms were found in the blood. The fever disappeared on treatment with synthetic medicaments. The bilateral ptosis and paralysis of the right external rectus muscle cleared up temporarily, after a diagnostic injection of prostigmine methylsulfate. During the next few days the myasthenic syndrome cleared up. The Kahn reaction of the blood of the patient and of the parents were negative. The fundi were normal, and the reaction to the Mantoux test was negative.

SAVITSKY, New York.

## Encephalography, Ventriculography, Roentgenography

MYELOGRAPHY WITH PANTOPAQUE AND A NEW TECHNIQUE FOR ITS REMOVAL. WENDELL G. SCOTT and LEONARD T. FURLOW, Radiology **43**:241 (Sept.) 1944.

Scott and Furlow believe that pantopaque (ethyliodophenylundecylate) is a satisfactory medium for spinal myelography. It is about as opaque and cohesive as iodized poppyseed oil; it has produced no reactions of importance, and its great advantage lies in the fact that it is much more easily removed from the spinal canal than is the iodized oil.

Sedation is induced with morphine before the examination. After spinal tap, 3 cc. of the medium is in-

stilled. The stilet is reinserted, and the needle remains in place during the entire examination. The usual fluoroscopic and spot film technic is employed.

To remove the oil, the patient remains in the prone position and the craniad portion of the column of oil is allowed to flow beneath the tip of the lumbar puncture needle. The stilet is removed, and the spinal fluid is allowed to bubble out without the syringe being attached. By forced expiration against a closed glottis (Valsalva experiment), the intraspinal pressure is increased; the column of oil becomes thinner and rises from 0.5 to 8 cm. in a cephalad direction. In this way the oil, under pressure, comes into intimate connection with the needle tip and flows freely from the needle. The Valsalva maneuver is repeated until all the oil is removed. Twenty minutes is required for complete removal, but *occasionally forty minutes is necessary.*

The authors were able to remove all but a few drops in 48 of 50 cases. The failures were due to intradural adhesions from a previous laminectomy in 1 case, and to lack of cooperation in the patient, in the other.

The need for myelography in suspected cases of herniation of an intervertebral disk varies with different neurologists and neurosurgeons. The authors believe that if the indications for surgical intervention are so convincing that the surgeon can assume full responsibility for the accuracy of his findings, myelography is not necessary. However, many men prefer support from the myelogram before submitting their patients to a major operation. Myelography is useful for patients with persistence or recurrence of pain after operation. It is also helpful in the positive identification of multiple protruded disks and may spare the patient unnecessary exploration of normal disks.

TEPLICK, Washington, D. C.

## Congenital Anomalies

ABORTIVE FRÖHLICH SYNDROME WITH DISEASE OF THE CEREBELLUM AND SPINAL CORD, POLYDACTYLY AND MUSCULAR ATROPHY: A NEW SYNDROME (?). AUSTREGESILO JR., Arch. brasil. de med. **34**:7 (Jan.-Feb.) 1944.

Austregesilo describes a variant of a degenerative disease of which he has not been able to find a case in the literature.

A white laborer aged 32, single, complained of progressive weakness in the lower limbs of seven years' duration. There were pains in the lower limbs of three years' duration, sexual impotence and a history suggestive of mental retardation. The testicles did not descend until the eighth year. The patient had 10 brothers and 8 sisters, all of whom were well. There was no consanguinity. A paternal grandfather had six toes on each foot. A maternal grandfather died at the age of 60, with paralysis of the lower limbs. One cousin had a deformed foot and another bilateral talipes equinovarus.

Examination revealed obesity, feminine distribution of hair, gynecomastia, kyphoscoliosis and bilateral polydactyly (six toes). There were dysdiadokokinesis, ataxia and dysmetria in both upper limbs; atrophy and muscular weakness were present in both lower limbs, especially the left. The flexors were more severely involved than the extensors, especially in the proximal portions. None of the tendon reflexes could be elicited. There was diminished sensation for superficial modalities, especially for temperature, in the lower limbs; these sensory changes were most pronounced in the extra toes; deep sensibility was spared. The superficial reflexes were normal; the Babinski, Rossolimo and Mendel-Bechterew signs were not elicited. Divergent strabismus was noted in the left eye. There was no retinitis pigmentosa; the fundi were normal.

This man had a forme fruste of Fröhlich syndrome, polydactyly, ataxia of the upper limbs and muscular atrophy of the lower limbs.

SAVITSKY, New York.

# Society Transactions

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

BYRON STOOKEY, M.D., *President, New York Neurological Society, Presiding*

*Joint Meeting, Nov. 14, 1944*

SYMPOSIUM ON INJURIES OF THE NERVOUS SYSTEM

**Presidential Address: Surgical Aspects of Peripheral Nerve Injuries.** DR. BYRON STOOKEY.

**Management and Treatment of Craniocerebral Injuries.** DR. LOYAL DAVIS, Chicago (by invitation).

The management and treatment of craniocerebral injuries received in battle and those received in civilian life do not differ in principle. That injury to the underlying brain is far more important than injury to the bone, that a laceration of the scalp should be cleansed, debrided and sutured accurately, layer by layer, with fine suture material, that indriven fragments of bone and metal or other foreign substances should be removed if they can be reached easily without producing further destruction of brain tissue; that fragments of shell should not be probed for if they lie deep within the brain—all of these are accepted basic considerations.

In September 1942 it became necessary to establish an organization for the treatment of craniocerebral casualties in the European Theater of Operations and at the same time to formulate general principles of surgical treatment which would not be too rigid and, too, would guide the younger and less experienced medical officers situated far forward. It was insisted on that early definitive care by experienced neurosurgeons was necessary for the successful treatment of compound craniocerebral injuries. Therefore, certain general hospitals in which well trained neurologic surgeons were stationed, so located that they were easily accessible to the lines of evacuation, both within England and from the Continent to England, were chosen as centers to which these casualties could be taken. It was predicated that unavoidable delay in evacuation would be compensated for by having an expert neurologic surgeon completely equipped with a suction apparatus, electrosurgical unit and other modern pieces of neurosurgical armamentarium, in a hospital so situated and equipped that final definitive treatment could be administered.

Definitive, or reparative, surgical procedures on craniocerebral injuries are designed to prevent or cut short wound infection either before it is established or at the period of inception and to restore function. Once established, infection is destructive of tissue and of life. Even if combated successfully, it may permanently preclude the restoration of function by the most skilful reconstructive efforts. Therefore the decision to close the scalp wound must always be based on an appraisal of the gross appearance and on recognition of the fact that craniocerebral wounds left open are easy prey to infection. This decision, it was argued, should be made by an experienced and recognized neurologic surgeon.

Further, it was established that neurosurgical teams should be assigned to evacuation hospitals, more closely situated behind the advance of an army, and be composed of younger surgeons well trained in the principles of surgery, and preferably with several months' experience on a neurosurgical service. It was believed that these men could be taught the essentials of the immediate treatment of a compound craniocerebral injury —that is, not to do too much, and not to do too little. In effect, they should cleanse the wound surgically, with emphasis on shaving the hair about the wound, washing the wound thoroughly with soap and water, removing superficial indriven fragments of bone, metal or debris, introducing sulfanilamide or sufadiazine powder into the depths of the wound, placing a sterile dressing over the wound, securing it in place with a crinoline or light plaster cast and providing the patient with sulfadiazine tablets to be taken during his transportation. In addition, it was believed that such young men would realize the importance of rapid evacuation for definitive surgical treatment and would, therefore, insist on by-passing several medical installations which had been created by armchair surgeons in the Medical Corps during peacetime. It was also advised that the surgeons of these auxiliary or itinerant teams could be sent farther forward to stimulate battalion and regimental surgeons to do likewise and, if possible, to bypass the evacuation hospital.

As a corollary to this line of reasoning, it was believed that such younger surgeons, devoid of ambition to become neurosurgeons later in civilian life, would not be tempted to do extensive, ill advised surgical procedures far forward, under poor environmental conditions, without adequate equipment and help.

It was emphasized that there are three essential approaches to the application of chemotherapeutic agents to war or to civilian craniocerebral injuries. First, the sulfonamide compounds and penicillin are not substitutes for the surgical excision of devitalized tissue; second, the sulfonamide drugs will permit delay in operation on the wound and minimize the chances of development of infection following careful surgical treatment of the wound, and, third, they will extend the scope of surgical treatment and make it possible to achieve a perfection in results previously considered impossible. From the results of experiments which were then under way in my surgical laboratory on the use of the sulfonamide compounds with gunshot injuries involving peripheral nerves, it was evident that unavoidable delays between injury and definitive surgical treatment could be bridged rather successfully by the judicious use of these agents. Particular attention was called to the use of a sulfonamide jelly, which could be introduced into the depths of a wound immediately after its receipt by the first medical officer who saw the patient, more effectively than the powdered drug could be dusted into the wound. These substances, then, were not considered as substitutes for surgical measures, but chemotherapy did open new and startling possibilities in management of craniocerebral injuries.

From Sept. 1, 1942 until May 1, 1943, 153 men with craniocerebral injuries were evacuated as soon after

injury as possible to four hospitals in England. In two of these hospitals a well trained and recognized neurologic surgeon was in charge, and in the other two were men who had completed a resident general surgical training, which had included a period of service in neurologic surgery. The compound craniocerebral injuries resulted from accidents which occurred while driving jeeps during the black-out and from fragmenting German Oerlikon 20 mm. shells which exploded within our bombers. The closed type of craniocerebral injuries was received in the manner common in civilian life, as well as in bicycling accidents during black-outs.

Ninety-nine men with acute craniocerebral injuries of the closed type, with or without demonstrable roentgenographic evidence of fracture, were treated conservatively and were got up and out of bed at the earliest moment and stimulated to perform light duties about their wards. Of these, 88.8 per cent were returned to their full duty; 5 per cent were returned to the Zone of the Interior; 2.2 per cent were still in hospitals for rehabilitation and, at the time of this study, 4.4 per cent were still in hospital under treatment.

Seven men had acute craniocerebral injuries of the open type which were of noncombat origin, with the dura mater torn, with the cortex exposed and injured or with subdural or subcortical hematomas. One was returned to full duty and 3 to limited duty in the theater of war. Two were returned to limited duty in the Zone of the Interior, and 1 had been sent to a rehabilitation hospital in the theater. Nine men had open craniocerebral injuries received in air combat, and all had metallic fragments driven far into the brain. One returned to duty in the theater, and 8 were sent back to the Zone of the Interior. Thirty-three patients complained of symptoms of the post-traumatic syndrome, and their injuries were classified as of chronic craniocerebral type. The majority of these men were treated primarily in other hospitals before they came under the care of one of these four qualified men, who recognized the importance of getting the patient out of bed as early as possible and of minimizing the nature of the injury to the head for prevention of the post-traumatic syndrome. However, 50 per cent of these patients were returned to duty in the theater of war; 15 were returned to the Zone of the Interior, and 1 was in a rehabilitation hospital. Six patients with old craniocerebral injuries incurred before they had entered the Army, all with damaged cerebral tissue or with osteomyelitis of the skull, were among this group. Three were returned to duty in the theater, and 3 were sent back to the Zone of the Interior, which none of them should have left.

It was not difficult to reduce the frequency of the noncombat compound craniocerebral injuries. Jeeps were driven during the black-out on wholly unauthorized missions, and the average American soldier was not accustomed to bicycling on a twisting, narrow English road during a black-out. The matter of the open head injuries sustained in air force combat was quite different.

That something might be done to prevent these injuries in whole or in part was emphasized by the fate of a Flying Fortress pilot. The co-pilot was more apprehensive of the exploding and multifragmenting, high velocity German Oerlikon 20 mm. shells than was the pilot. He therefore pulled down over his regulation flying helmet the outside, or metal, portion of the regulation issue steel helmet. Without its interliner, this part of the helmet weighs 2 pounds (907 Gm.), and this, together with the fact that it restricted backward movements of his head and cut off a considerable portion of his temporal fields of vision, made it impractical for the pilot to wear. An Oerlikon shell penetrated the nose of the plane; the initial velocity was reduced, but its fragments, varying in weight from 1 mg. to 20 Gm., with the effective fragments weighing between 10 and 50 mg., numbering thousands and traveling at a velocity of about 500 meters per second, exploded between the pilot and the co-pilot. The right side of the pilot's skull was penetrated by many small fragments, which left no visible evidence of laceration of the scalp or of fracture of the bone. He became unconscious immediately, and his co-pilot, sitting by his side in the field of the burst, but with his helmet protection, brought the plane in. The pilot had left hemiplegia and left homonymous hemianopsia; the co-pilot had three minute holes in the helmet.

As a result of work with this type of injuries in airmen, it was evident that, besides furnishing adequate protection, a helmet should be designed to fit the head closely and should be comfortable, light and of such construction and appearance as to be a desirable piece of protective clothing for the airman. An acrylic resin product which could be molded in segments to fit the skull; which could be placed within a leather flying helmet; which afforded one-third more protection per unit of weight than does 1 mm. of manganese steel, when tested with an electrically fired 50 mg. steel ball; which was an excellent nonconductor of heat and cold; which had a Brinell hardness greater than gold; which fragmented when struck at right angles to the force; which had an impact resistance of 0.1 to 0.3 foot pound, a tensile strength of 9 to 12,000 pounds (41. to 5,450 Kg.) per square inch (6.45 sq. cm.) and a flexural strength of 12,000 to 14,000 pounds (5,450 to 6,350 Kg.) per square inch; which would absorb less than 0.5 per cent of water by weight after immersion for seven days; which would not burn with a flash; which had no tissue reaction, and which would reduce ambient noises around ear phones, such a product would produce a finished helmet weighing 1 pound 8 ounces (680 Gm.). This helmet was presented for consideration and adoption through channels some time ago; but in the meantime airmen continue to be unprotected because they refuse to wear the heavy steel helmet during combat in the air.

Evidence from other sources shed light on the management and treatment of craniocerebral injuries and aided materially in strengthening the policies and organization which had been laid down but which had not undergone the test of combat conditions. For example, the Canadians working at Neurological Hospital 1, at Basingstoke, England, received for treatment 14 men with penetrating craniocerebral wounds after the Dieppe catastrophe. Of these patients, 12 received definitive neurosurgical care within forty-eight hours after injury, 1 after three days and 1 after five days. Only in the last patient did infection of the wound develop. Three of these 14 patients died of general circulatory collapse, and 2 had a permanent residual hemiplegia. Sulfonamide powder was introduced into all of the wounds at the time of definitive treatment.

Of 128 patients with gunshot wounds of the head admitted to St. Hugh's Hospital for Head Injuries at Oxford, England, in a nine month period, 49 were invalided out of the service. Cairns stressed that infection of craniocerebral wounds does not usually occur from the bullet or the shell fragment but comes from the patient's skin or the surgical attendants. A report from Germany in January 1943 indicated that early in the war, when the Germans had complete domination

of the air over the Continent, they flew a neurosurgical operating unit from one combat area to another. This was the reverse of getting the patient quickly into the hands of a neurosurgeon. This practice has since been discontinued. Tönnies and Sanger believe that four days between injury and definitive treatment is the maximum interval for a successful outcome, and it is assumed, since they did not definitely so state, that this is without the use of the sulfonamide drugs at the time of the injury.

Even more conclusive evidence of the success of rapid evacuation of patients with craniocerebral wounds to a neurosurgeon, properly equipped, situated in as favorable an environment as possible and with sufficient aids to carry out good postoperative treatment, came from Major Peter Ascroft. All will remember his recital of experiences with the British armies in North Africa. Ascroft reported on 516 patients, the series representing two years' experience in the Middle East. Of these patients, 292 had laceration of the dura and 44 died, a mortality of 15 per cent. Of the remaining 226 patients, 124 were returned to duty, and 93 were invalided out of the service because of the head wound. His experience showed that the results of primary operations in a general hospital carried out as late as forty-eight or seventy-two hours after injury are at least as good as the results of operations performed in more forward areas, where conditions are difficult, within eight hours after injury and are better than the results of operations done from nine to sixteen hours after injury. Ascroft stated the problem clearly when he said: "We believe it is better not to operate in forward areas, provided that the patient can reach a fully equipped base hospital within forty-eight to seventy-two hours of injury. That is not to say that there is any merit in delay for its own sake; the sooner a head wound is operated on the better, always provided that facilities are available for a complete operation and proper after-care." In other words, the results which he, an experienced neurologic surgeon, could obtain by taking his mobile and well equipped unit to the front were much less favorable than when it became possible to evacuate and transport the patient rapidly to a general hospital where he and his teams were situated.

In addition to these experiences, I had the opportunity of seeing at first hand the organization of the Red Army Medical Corps and the methods which it used to manage and surgically treat craniocerebral injuries. The essential principle on which it based its reported excellent results was the utilization of competent neurologic surgeons in hospitals placed as far forward as the evacuation hospital is situated in the United States Army, completely equipped and staffed to perform definitive neurosurgical operations. There was no problem of fixed tables of organization and supply to surmount before electrosurgical units, suction apparatus and x-ray equipment could be placed as close to the injured man as the tide of battle would permit.

There were 16 neurologic surgeons on the various Russian fronts, with 3,200 beds at their disposal, and three large hospitals in the rear, or Zone of the Interior, as we would designate it, with 3,700 beds. The latter hospitals were closely affiliated with medical institutes (schools) where civilian physicians cooperated closely with the army in making studies of the multitudinous problems which concern the future progress of the treatment of neurosurgical injuries. Procedures learned by experience were passed on to the younger surgeons by such close correlation of effort as to obviate the necessity for the young surgeon to concern himself with discovering already proved methods of technic, to the exclusion of recording observations on clinical material which may never again be equaled for study.

There were other interesting features of the Russian organization for the care of craniocerebral injuries, such as segregation of patients to separate wards, even as far forward as a mobile field hospital, and the insistence on complete records, which accompanied the patient from the time he was first examined by a medical officer until he arrived in a hospital in the rear. Even more striking was the flexibility of organization which permitted a young neurologic surgeon, like Graschenko, to go forward and treat casualties in an advanced area, while the other half of his team remained in Moscow and cared for patients who had been treated and evacuated by them while they served at the front and Graschenko was in the rear hospital. This line of evacuation and continuity along one agreed-on policy of treatment, together with careful records, will make it possible to report studies of craniocerebral injuries received in battle which we in this country cannot duplicate.

This direct and immediate control of the surgeon general of the Red Army over all the activities and responsibilities of the medical corps, without interference from the echelon above, made it possible for Graschenko, for example, to study the course and influence of infection on the healing of craniocerebral wounds and the clinical and bacteriologic results of the application of the sulfonamide compounds to craniocerebral injuries, with an auxiliary microbiologic laboratory staff which accompanied his surgical unit to the front.

Under field conditions, Graschenko studied 100 cases of craniocerebral injuries bacteriologically. In 20.3 per cent of the cases pathogenic organisms were found. In 12.4 per cent sporogenic (putrefactive anaerobes) were present; in 24 per cent aerobic organisms were cultured; in 26.8 per cent coccic infections were present, and in 16.5 per cent miscellaneous organisms were found. Cultures were made from forty-eight to seventy-two hours after injury in a total of 720 cases, and in only 2 cases were the cultures sterile. However, the largest number of the wounds healed primarily without suppuration.

After three to four weeks Graschenko found that the wounds showed a flora of pathogenic anaerobes in 12 per cent of cases, aerobes in 20 per cent, cocci in 70 per cent and putrefactive anaerobes in 8 to 10 per cent. Of the 20.3 per cent of patients in whom pathogenic anaerobes were found, 1.4 per cent died in from six to seven days of severe gas bacillus infection. Subacute anaerobic infections of the brain were found in cases of large cerebral fungi, and of 12 patients with such infection, 9 died. Of 32 patients with chronic anaerobic infection of the brain, 10 died. The course of their illness was long, from three to four months, and often encapsulated abscesses were formed, which might open onto the surface or into the ventricles, with the production of severe meningitis. Of 34 patients with mild anaerobic infection of the brain, none died. Graschenko uses a polyvalent serum in prevention of gas bacillus infection of craniocerebral wounds which contain Clostridium histolyticum, Clostridium perfringens, Clostridium oedematiens or Clostridium oedematis maligni.

These, then, briefly were the factors, together with experience in civilian practice, which led to a statement of the following creed of principles concerning the management and treatment of craniocerebral injuries, a creed which applies alike to civilian and to battle casualties.

The scalp is richly supplied with blood vessels and offers considerable resistance to infection. The intact dura mater is a good barrier against the spread of infection, and on the whole the meninges have the power of localizing infection. Provided the products of injury and infection are not allowed to gather under pressure, brain tissue resists infection fairly well.

The gentlest surgical procedure in the most skilled hands is damaging to some degree, and damage to the brain is irreparable. Surgical procedures cannot be carried out within the skull effectively without an electrosurgical unit, suction apparatus, proper x-ray equipment, adequate and proper instruments, facilities for the skilful administration of various types of anesthetics and good nursing teams.

Assessment of the condition of a patient with a craniocerebral wound should include consideration of the depth of coma, the presence or absence of shock, the exact nature of the head wound and, particularly, the presence or absence of other injuries. Shock is seldom severe with head wounds, and when present it is usually due to a loss of blood which can be made up quickly. In the case of compound craniocerebral wounds, roentgenograms of the skull are of great value, particularly in the absence of good clinical notes, and often of any kind of record, in judging the depth and nature of indriven fragments of bone and metal and the condition of the dura mater and brain.

Incomplete operations are more dangerous to the patient than the few hours of delay necessary to evacuate the patient to a competent neurosurgeon in a properly equipped environment. There are only three reasons for retaining a patient and performing an operation under adverse conditions: (1) severe shock—after he has been treated for shock the patient should be evacuated as quickly as possible for a definitive operation; (2) intracranial bleeding and compression of the brain, or other bodily injuries requiring emergency surgical intervention, and (3) lack of opportunity to get the patient to a properly equipped center or hospital within forty-eight to seventy-two hours after injury.

The urgency for operation on craniocerebral wounds depends on whether or not the dura mater is penetrated and on the degree of damage to the brain and the number and character of the indriven fragments. There should always be a detailed examination of the central nervous system, with a record of the state of consciousness in terms of the presence or loss of important reflexes and the response to pain, noise or other stimuli. There must always be an examination for other injuries. Wounds of the face, particularly of the orbit, often involve the skull and brain, and the ear drums may be ruptured, with bleeding, by blast, in contrast to civilian injuries. Badly mangled extremities may lead to an inconspicuous head wound being overlooked, just as a serious head wound may lead attention away from wounds of other organs.

Local anesthesia cannot be used as often as one might think possible, and, though sodium pentothal proved very efficient, it is absolutely necessary that good breathing be established before draping of the head and face is completed. Careful shaving and cleansing of the wound and the field of operation are absolutely essential, and the application of colored antiseptic does not take the place of meticulous cleansing of the wound with soap and water. Haste and skimping in the preliminaries do not save time, and carelessness in preparation makes for bad operations.

Scalp incisions vary with each type of wound, but certain general points apply. The edges of the scalp wound should be excised as narrowly as possible, and incisions should extend the wound, if necessary, to give access to the underlying lesion. Missiles destroy the scalp more than ordinary injuries in civilian life, and often the edges of the wound and the bone are burned by high velocity metal fragments. There may be a small superficial wound in the scalp and underlying extensive destruction of the deeper layers. Fractures of the bone may be of all sizes and shapes, and all detached fragments of bone must be removed to discourage the infection and to expose tears in the dura mater or damage to the brain. However, removal of bone must be conservative, and excision of bone *en bloc* should not be done. Local bone decompression is unnecessary.

The dura mater should never be opened if it is intact unless there is an immediate threat to life from a subdural blood clot. If torn, the edges of the dura should be trimmed, but, if possible, removal of large portions should be avoided. The dura may be dissected away from the inner table of the bone, for foreign material may be hidden between the dura and the bone. Indriven fragments of bone have been proved to be present in the majority of cases of abscess following injury to the brain. This is not true of metallic fragments, which usually penetrate deeper than fragments of bone but are probably partially or totally sterilized by their own heat. It should therefore be the object to remove easily approachable fragments of bone and metal, hopelessly damaged superficial brain tissue, blood clots and foreign matter, by gentle suction if necessary. Often the removal of a surface plug of foreign material of this kind will allow more deeply placed debris to well up and out of the wound in the brain. Probing and searching for deeply placed metallic fragments should never be carried out. Good hemostasis, which can be obtained with silver clips; electrosurgery, and use of fibrin foam are essential to good results.

The introduction of sulfanilamide or sulfadiazine powder into the tract and on the surface of the cerebral wound should be a part of the surgical treatment. From a study of experimental gunshot wounds of peripheral nerves and from observations on wounds received in the North African campaign, I believe that the introduction of a sulfonamide jelly into the depths of the wound immediately on its receipt will make it possible to carry out definitive surgical treatment more satisfactorily and with far less danger of the development of a suppurative wound. There is evidence that use of sulfathiazole in wounds of the brain does not have the danger that earlier experimental and clinical reports indicated.

The practice of young, inexperienced surgeons who have been dealing with craniocerebral wounds in certain theaters of war, without the opportunity of guidance and consultation with an experienced neurologic surgeon, of using fascial grafts from cadavers and other diabolically ingenious methods of closing dural tears in freshly received and potentially infected wounds is a comment on poor organization. If the scalp wound can be approximated without tension, it should be closed without drainage. Ofter a drain is necessary when it becomes impossible to close the scalp wound because of a large loss of tissue, but it must be remembered that continued exposure of the brain in an open wound is always followed by infection. Deliberately to pack open a craniocerebral wound with petrolatum gauze, as has been done in mistaken adherence to a general

directive about war wounds, without using good surgical judgment in opposition to the directive, is, like the theft of cadaver tissue, a reflection on medical organization, as well as on inferior surgical education. Certainly, plastic repair of the skull by any method has no place in the treatment of acute craniocerebral injuries.

Finally, nursing care must be intensive, intelligent and enthusiastic. Sufficient help must be provided to turn the comatose patient frequently, to care properly for the skin, to see that he gets food and fluid, to prevent the extreme restlessness which is produced by a distended bladder or a wet bed and to control sedation carefully, and, last, the proper attitude must be maintained toward the patient's injury, so that he may be returned quickly to activity around the ward and his final rehabilitation may be successfully and speedily accomplished.

**Psychiatric Aspects of Injuries to the Nervous System.** LIEUT. COL. WALTER O. KLINGMAN, Medical Corps, Army of the United States.

The problems produced by injuries to the nervous system have become increasingly important with the progress of the war. Interrelating problems of appraisal and treatment from the surgical, neurologic and psychiatric standpoints present themselves, particularly with respect to the large group of disturbances that are labeled psychoneurosis, postconcussion neurosis, traumatic neurosis or compensation neurosis.

Because of the difficulties encountered in differentiation of the traumatic and the post-traumatic reactions, classifications of the psychiatric disturbances in connection with injuries of the nervous system have not been very satisfactory. War injuries introduce complications which differ in some respects from injuries to the nervous system sustained in civilian life, owing to the combination of natural anxiety with war stress, grievances, predisposition and circumstances of exhaustion or fatigue, particularly when there is also a structural change in the nervous system.

The acute mental symptoms of cerebral injury are those concerned with disturbances of consciousness, ranging from states of transient interference, in cases of mild injury, to profound coma, in cases of severe injury. In the return from stupor to normal consciousness, automatism and states of dissociation may be difficult to differentiate from other states of complete dissociation in the combat area, particularly when there is no external evidence of a head injury. In some cases of mild injury, momentary stages of confusion or of daze may be followed by automatism and may, in the combat area, lead to confusion and make for unintelligent behavior and incomprehensible actions. In other cases of mild injury without loss of consciousness there may be delayed collapse, after minutes or hours, or some intermittent confusion, with or without automatism.

In the cases of severe cerebral injury recovery does not always follow, and signs of local damage, specific defects of the nervous system and disturbances of function may result. Alterations in memory, orientation, perception, imagination and emotional attitudes may occur, and unstable behavior patterns may result. Some of these functions may be permanently altered, particularly in elderly and in arteriosclerotic subjects.

In other cases it is difficult to evaluate persisting symptoms when recovery stops short of being complete, particularly in the absence of signs of demonstrable lesions.

The most common residual neurologic syndrome is that of headache, dizziness and emotional instability, and in many cases the picture suggests that in the syndrome or in the origin of the emotional instability there is an interplay of physical and psychologic factors. At this time it is considered impossible by particular clinical criteria to distinguish between a true psychoneurosis of psychogenic origin and one having organic cause, for any symptom may have either factor as a basis.

Definite improvement in the psychiatric management of cerebral injuries in the immediate post-traumatic state has been recently introduced. Graduated programs of activity are frequently started within twenty-four to seventy-two hours after the patient regains consciousness, with early return to light Army duties in two weeks. This therapy attempts complete divorcement from the idea that the injury is serious and that certain symptoms are to be expected. It eliminates the period of incubation, in which the patient meditates on the suffering and derangement of his life. The Army hospital as a rule is not convenient for frequent visiting by well meaning relatives, friends or claim agents. In the combat area, however, the element of secondary gain may be a potent factor with which to contend. The incorporation of convalescent and rehabilitation programs in many Army hospitals must also be credited with much of the beneficial reversal of results and of methods of management now in vogue. In this early phase of activity there is introduced the psychologic help calculated to strengthen the ego by persuasion, strong suggestion, reidentification and stimulation of the ego ideal.

Despite this, however, physiologic consequences of the trauma in many cases affect the function and structure of the brain to the extent that they offer material for the neurosis or activate a latent or an active neurosis of severe degree.

When this results, the emotional attitudes change; the symptoms assume bizarre qualities, and it is time then to evaluate the signs and symptoms and analyze the psychologic and physical factors in the symptom complex. Each case must be studied and treatment instituted according to its merits. Painstaking neurologic examination, evaluation of emotional factors, psychologic tests and electroencephalographic and pneumoencephalographic examinations may be necessary. In this, evaluation of the emotional factors and methods of combating them have likewise profited by experience in this war. Narcoanalysis, narcosis therapy and narcosynthesis have been used in civilian practice for many years, but their free use has been necessitated and forced into the foreground by the urgent demands for brief, quick therapy in the armed forces. Application of these technics in the prevention and treatment of neuroses following injuries of the nervous system has added understanding of the conflict between the unconscious sources of anxiety and the ego forces and has aided in the evolvement of short term technics derived from psychoanalytic principles. Time is gained by this in that the period necessary to work through resistance is eliminated and uncovered anxieties can be tolerated without lengthy strengthening of the ego. Narcoanalysis, followed by psychotherapy as the patient recovers from the narcosis, results often in dramatic release of the unconscious psychologic tensions, strengthens the ego forces and decreases the severity of the superego pressure. This is particularly true of patients with latent anxieties and resentments dating back to earlier periods of life.

Patients with specific handicaps require special consideration through prolonged rehabilitation programs.

Their worries about cure, livelihood, bodily helplessness and future disturbances of social and economic nature are real and offer a tremendous challenge for life in the future without dependence on family or country.

Another clinical picture presented by injury to the cerebrum is that associated with subdural hematoma or effusion. The psychiatric syndromes encountered may be of two types. The most frequent is that of marked retardation in intellectual activity and personality interrelationships, a flat emotional tone, impaired attention and slow responses. Approach to life situations is superficial. In the other, and less frequent syndrome there is a more classic picture, usually associated with the organic reaction types, with impairment of inhibition or restraint, facetiousness, motor restlessness, a labile and explosive emotional tone, poor judgment, undue productivity and expressions of hostility, distractibility, memory failure, perseveration and circumstantiality. Minimal neurologic signs are the rule, and a pneumoencephalogram may be necessary for a final diagnosis.

In another group are the debatable cases in which the relationship between head injury and mental disease is not so clear but in which the trauma may have served to precipitate the psychosis, such as schizophrenia or manic-depressive psychosis, neurosyphilis or other disorder rather than act as the direct etiologic agent.

In other cases, however, the organic mental syndromes following head injury can be delineated as definite post-traumatic psychopathy. In this group there is absence of any signs of a psychopathic state prior to the injury.

Out of wartime experiences have arisen certain facts for emphasis. Many persons who have a disabling neurosis after head injury suffer from a latent or active neurosis before exposure to military life or from a neurosis incidental to the war experience. Several valuable psychiatric factors have been introduced in the management of injuries of the nervous system by the experience of this war. Prophylactic psychotherapy during the management of the immediate post-traumatic phase has reduced the prospect of persistent disability. Application of short term technics of treatment based on psychoanalytic principles, followed by sound rehabilitation programs, has been most helpful in the treatment of injuries of the nervous system with subsequent neurotic expressions. Diagnostic and prognostic aids from psychologic testing, electroencephalography and air encephalography may be necessary in the full appreciation of structural damage or the psychoneurotic state. Patients with mixed pictures of organic and functional disturbances require management according to the merits of their particular cases, through prolonged psychotherapy, programs of rehabilitation or the protective environment of institutional life.

### DISCUSSION ON PAPERS BY DRS. STOOKEY, DAVIS AND KLINGMAN

DR. FOSTER KENNEDY: To discuss adequately these three papers would be to go over the whole of medicine and most of war. From Dr. Stookey's paper, I came to the conclusion that every generation must learn from its own experience; this is true of all men, and not of members of the medical profession alone; it is too bad that it is so, for writing was invented to teach the *next generation. I do not think that we physicians* go back far enough in our reading. I was much surprised to come across the report of an autopsy on the brain written by my grandfather sometime in 1840 which would have borne excellent comparison with any similar report today. I had to go back to the *Lancet* of 1830 to get modern advice regarding water balance from a man named Harrison, who had ideas on the treatment of cholera which had to do with water balance. I think that Dr. Stookey believes, too, that if the younger men would do what we older ones do not do—go back farther—they would learn more. It is the modern notion that everything one knows occurred the day before yesterday. It certainly did not, and we physicians would understand better the basis of our knowledge if we went back farther in our reading. It is said, "Every book that is written is out of date in five years, and no medical magazine is worth anything if it is a week old." This is nonsense. Such productions are the work of men earnest, anxious and eager; if we are going to continue our constancy of effort, we shall have to ask our students and our young medical officers to go back to former experience in order to learn about the present. There has never been a better description of certain forms of war wounds (and causalgia is one which is a bugbear today) than that written by Weir Mitchell during the Civil War; I wonder how many present day medical officers have read *his description of causalgia. We certainly cannot* learn any more about causalgia from modern medicine.

It is good to hear Dr. Stookey speak roundly against the "funnel" idea of nerve union. I think that idea sprang from the general tendency to diagrammatic oversimplification. It seemed better to put the nerve fibers in a "directing" funnel and to say that then they would be all right. I am sure the concept is fundamentally unsound, and I am glad Dr. Stookey has said so. There are many more ways of killing a cat than skinning it. It is possible that many nerve injuries can be dealt with better by plastic surgery rather than by the best of nerve grafting. For instance, many facial paralyses can be better handled by dealing with the muscles involved than by operating on the nerve implicated. This idea might have many applications in treatment of peripheral lesions due to the war. Dr. Stookey spoke wisely against nerve stretching. To subject the most highly developed tissue in the body to a traction which it cannot possibly sustain and expect it to function afterward is to err in thinking. It is not only an error in technic but originally an error in thought.

I was glad to hear Dr. Stookey speak of Huber, who has by no means received the credit due him; he did basic work in this field.

I liked Dr. Stookey's idea about nerve banks. If grafting is necessary, nerve banks will be a necessity, to have vital nerve tissue to place in situ at once.

Dr. Loyal Davis told us of sulfonamide drugs, which, unfortunately, were not available in the last war, with the result that one might see then, as I did, 30 or 40 cases of abscess of the brain in one hospital in one day. That horrible period, apparently, is passing and has almost passed. Dr. Davis did not speak, however, of the habitual use of phenobarbital in cases of compound injury affecting the brain. I think every soldier should be sent from the front area in which he has been wounded with a ticket that he has been given phenobarbital and that he should be given phenobarbital, ½ grain (0.032 Gm.) three times a day, for the next year. This medication should be started at the place where he is wounded. It is important to lower the *reflex activity of the brain when it has been grossly* injured, as is the case with a wound.

About three years ago, in Washington, D. C., I wrote a memorandum urging that it be made compulsory for every American soldier who rides a jeep, a tank or a motorcycle to wear a crash helmet, and I

led a small campaign in behalf of the idea. I do not know whether it has been made an official order or not. It should be. Certainly, in World War I I got very tired of seeing motorcycle dispatch riders with fractured skulls. It is a lamentable waste of young life and could easily be avoided by the compulsory adoption of crash helmets. Dr. Davis gave you an example of what body armor, put on in no matter what spirit, can do in the preservation of life. I am glad to know that body armor is coming back. Certainly, armor of the middle torso and armor of the head can be used which will reduce by half the number of casualties that might occur in both air and ground warfare. The vast majority of men are not destroyed by great bomb damage; they are defeated by fragments. These fragments, in turn, can be combated by proper body protection. Not enough care is given by the head of the medical corps in any army to the kind of protection than can be afforded the soldier.

I was much interested in Dr. Davis' comment on Russia—in the continuity of medical opinion from the front line to the rear. I do not know how that could be produced in this country unless there can be obtained continuity in education, continuity of experience and, so, identity of opinion. I am sure that in technic it is a great advantage to have that identity of opinion; by it the sick man, the injured man, can be given standard treatment from the place where he is hurt to the place where he is finally going to get well or die. This is an advantage. I am not sure, however, that in order to reach it one would not have to give up more in the way of flattening out the differences by which this country lives than one would gain for the sick man. However, that is a question with philosophic, political and sociologic implications, which is not to be taken up here.

Colonel Klingman's discussion of unconsciousness interested me very much. No one knows what consciousness is, or unconsciousness either. Jefferson's paper read before the American Neurological Society (*Tr. Am. Neurol. A.* **79**:13, 1943) was, I thought, enormously illuminating, as is Denny-Brown's work on concussion. Certainly, one knows that a man shot through the frontal lobe with a revolver bullet may remain entirely conscious but that if he is hit on the back of his neck with a sandbag, he goes out instanter. Denny-Brown seems to have demonstrated that this is due to movement of the brain in its box induced by the blunt instrument, in contrast to the lack of movement of the brain in the case of the fast-speeding missile. So the government of consciousness is mesencephalic and not cortical. This is something that ought to be given wider recognition. It has been so much taught that the cortex is the highest instrument that the responsibility of the cortex for consciousness seems to have been accepted, whereas the real control is mesencephalic. One may "think" with the cortex (though I do not know that), but one certainly is "governed" by the hypothalamus and the midbrain. One's ability to remain conscious depends on the dominance of the mesencephalon.

Colonel Klingman, I think, wisely pointed out that "the future" will sometime later loom large in the thought of the man who has been hurt in the head, that is, in the place in which he seems to himself to live. Every man is more concerned about an injury to his head than to "some outpost of empire," such as his arm or his leg, or even to some other place he does not know much about, his torso, for example; but an injury to his head produces emotional effects which have to be considered. The idea of a compensation neurosis is not entirely foreign to the soldier who, having had an injury to the head, looks to the future: Who is going to take care of him? Once I was asked what a civilian compensation neurosis was. I said it was "a state of mind, born out of fear, kept alive by hope of gain, stimulated by lawyers and relatives and cured by a verdict"; and while those words do not apply exactly to some soldiers, they apply to the general idea of the veterans' bonus. I am glad to hear that the medical officers in this war, like Colonel Klingman, are aware of this situation: It has a great deal to do with the future happiness of the soldier and the stability of the country. Colonel Klingman used a phrase which was enormously important—the "inherent adaptive capacity" of man. One may talk as much as one likes about the right technics and about what one will do for this man or that man, but the future of every human being, soldier or civilian, depends on his "inherent adaptive capacity."

DR. JOSEPH E. J. KING: I consider it a great pleasure to be here tonight and to have had the opportunity of listening to this splendid symposium. I wish to say that Dr. Stookey's address, on peripheral nerve injuries, is the best I have ever heard. Dr. Stookey, who had charge of the neurosurgical service at Fort Henry during World War I, has done a great deal of work on peripheral nerve injuries and has contributed a fine monograph.

I was interested in hearing his historical review of the treatment of nerve injuries, especially what he had to say about Dr. Weir Mitchell, Dr. Keen and others; it is astonishing that since the days of the introduction of aseptic surgery and of Billroth and the development of all sorts of major surgery, even brain surgery, the surgery of the peripheral nerves has been so backward, even up to the first world war. A rather good textbook on surgery published in 1914 or 1915 advocated splicing the nerve by merely turning down a portion of it, just as in a tendoplasty. I think all that is known about peripheral nerve surgery dates from the last war. I believe that the experience of the surgeons in charge of the various hospitals in that war was about the same. They saw about the same things. They performed about the same operations and obtained about the same results, and I do not know of any one who had any particular, unusual tricks that permitted better regeneration of these nerves than any other man had. Knowledge seemed to be widespread, general, and their opinions were collective and in agreement.

I have little to add to Dr. Stookey's presentation; perhaps I might mention a few details which he did not have time to consider and of which he has seen hundreds of instances. All of us in the first world war were impressed with the much greater disability of the whole limb, as well as the greater local disability, in cases in which the blood vessel was injured, with the associated purplish tinge or plum color of the skin of the limb and, in the case of the arm, the tapering fingers. In such cases my associates and I obtained very poor results. The best result from a nerve suture that I ever saw was in a case in which we divided the ulnar nerve beneath the hypothenar eminence into its two branches so that we could suture the motor and the sensory division separately. I cannot give any statistics and shall only mention my impressions and recollections of our worst injuries. They were the major injuries of the brachial plexus, and in cases of such lesions an attempt was made to free and suture the trunk, which sometimes could hardly be found.

Neurolysis of a brachial plexus gave poor results in our hands.

In general, practically the only good result we obtained was in cases in which the nerves could be sutured together, end to end, without tension, and in fairly decent tissue, with proper splinting. If the suture was not accomplished under those conditions, we did not expect a good result, and we did not get it. That does not mean we got no good results with our sutures, for some were rather good, some were fair, some were middling but some were poor. Perhaps the best results were obtained with the musculospiral and the radial nerve, possibly because these nerves are chiefly motor. The poorest results were obtained with the brachial plexus, and we got fair results with the median, the musculocutaneous, the ulnar and the sciatic nerve and its branches. In some cases, because of loss of substance, the nerve ends can be brought together only by transposition. Only once, in a case in which the ulnar, median and musculocutaneous nerves were divided, with considerable separation of the ends, did Dr. Frazier seem unable to bring the ends together except by resection of the humerus. He resected about 3 or 4 inches (7.5 to 10 cm.) of the humerus of the extremity involved and was able to approximate the ends of these nerves nicely. I cannot tell you about the final result, because I was not able to follow the case.

I should like to make a commendatory remark about our brace department. Dr. Robin Buerki devised some simple and very efficient splints, which prevented paralyzed muscles from becoming overstretched. Another phase of the work which I should like to commend was the splendid occupational and physical therapy department at Fox Hills, where the good women worked day in and out, for weeks and months, encouraging the patients to have confidence, courage and faith.

Dr. Stookey's comments on grafts are pertinent. We had only 6 cases in which grafting was done. In each instance there was also major destruction of the soft parts. The nerves could not be brought together; so trellis grafts were used. The massive scar tissue resulting from healing of wounds with such gross destruction of soft parts, in which the grafts were placed, probably choked off the grafts and prevented downward growth of the nerve fibers. This fact no doubt accounted for the poor results. All the grafting was done by Dr. Frazier.

The establishment of a nerve bank, of which Dr. Stookey spoke, making available longer nerve sections, by which the gross areas of scar tissue could be bypassed, might permit better results.

I enjoyed Dr. Davis' paper—an authoritative paper—and he can speak authoritatively. His opinions are not mere hearsay, for he was a member of a committee which visited various battle fronts and obtained his information firsthand. I agree with every word he said except that I think the removal of a mosaic of bone, such as Dr. Cushing advocated in the last war, might be of use with certain injuries.

For treatment of infection of the brain substance of several days' duration, a Mikulicz tampon of penicillin gauze or iodoform gauze, as we have used it in infected, necrotic and purulent wounds of the brain which were not yet abscessed, has worked out very well. I should like to ask Dr. Davis about the intrathecal use of penicillin, for instance, when the ventricle has been perforated and there is gross infection of the brain. The results of treatment of various types of meningitis with penicillin is known, but I have not heard any one speak with authority on treatment of the perforated wounds of the ventricle with this substance.

I should like also to ask Dr. Davis whether Cobl Pelcher's work on animals in which he used variou types of sulfonamide drugs and found that some were injurious to the brain tissue has been borne out by experience in the war.

I am unable to discuss Colonel Klingman's paper intelligently, but I am glad to have heard it. I am glad to hear of the great lengths to which the Medical Department has gone in this war to get men with cranial injuries out and around. I must say that our attitude in the last war was that a man who had been shot in the head was not quite, but almost, relegated thereafter to the world of useless people. The men were not encouraged to overcome their disability to the extent that they are now. The vetefans' hospitals are still full of these poor fellows.

DR. JEFFERSON BROWDER, Brooklyn: I should like to point out that facial nerve grafts will heal even if the wound is infected. I have had experience with cases of this condition. It seems to me that considerable information might be derived from a more careful study of such cases. With respect to peripheral nerve injuries, my personal observation has been that, although a graft may not serve as a channel for the downgrowth of somatic nerve fibers, it will serve as a bridge for the downgrowth of sympathetic fibers. That is exceedingly important, particularly with the tibial nerves. I have had experience with cases in which, after a graft, ulceration of the sole of a foot healed and remained healed, although one could not demonstrate any return in somatic function. So even if one is defeated on one score, a graft of this character serves a useful purpose.

I should like to ask Dr. Davis a question in conjunction with Dr. King's: It is true that the purpose of all definitive treatment of open wounds of the brain is to convert them into closed wounds. If the operation can be carried out without infection, there is only the general cerebral insult to be dealt with thereafter. What has been the recent attitude toward wounds that break open after they have been closed primarily? Certainly, some of them do break open and require further consideration.

Dr. Klingman spoke of shock in association with trauma to the brain. It has been my experience that the so-called shock associated with cerebral injury, exclusive of the shock resulting from hemorrhage or injury to other parts, is not true shock; in other words, it is not characterized by the rapid pulse, the low pressure and the pallor and sweating. It is observed as pallor and sweating without the acceleration of pulse and often without reduction in arterial pressure. I should like to ask Dr. Klingman whether he has similarly observed that the shock associated with cerebral trauma without complicating factors, such as hemorrhage and injuries to the extremities, has been as I have stated.

DR. LOYAL DAVIS, Chicago: In answer to Dr. King's question: To my knowledge, the only results of the use of penicillin for craniocerebral injuries are those carried out by Cairns and Florey in Sicily in the treatment of about 200 men with combined craniocerebral injuries. As far as I know, the report of their work has not yet been published. However, I observed the use of penicillin injected intrathecally and introduced into the ventricle in a case of meningitis following a combined craniocerebral injury. The results were remarkable, in view of the fact the condition was resistant to the sulfonamide drugs. The statement that I made about sulfathiazole therapy came from Ascroft, who used the drug in the Middle East without the ill effects which other investigators have reported. In answer to Dr.

Browder, I can only say that I have seen primarily closed wounds, clinically cleansed wounds, break down from infection and then make a secondary closure, followed by satisfactory healing without suppuration. However, sulfonamide compounds were used in the wounds locally and given by mouth at the time of the secondary closure.

LIEUT. COL. WALTER KLINGMAN, Medical Corps, Army of the United States: I wish to thank the various discussers for their comments. In reply to Dr. Browder's question about the nature of the shock, I must confess that my military experience with shock has been confined chiefly to the accidents which have to do with flying. As you know, such accidents are probably the most violent of physical injuries, and many of them are associated with fractures or injuries in parts other than the head. However, it has been my experience in cases in which there has been simple head trauma, with no other fractures or injuries that could be responsible for surgical shock, as it is understood, that there is sometimes no apparent relationship between the disturbance of consciousness and the presence of what is ordinarily described as surgical shock.

# Book Reviews

**François Magendie: Pioneer in Experimental Physiology and Scientific Medicine in XIX Century France.** By J. M. B. Olmsted, Professor of Physiology, University of California. With a preface by John F. Fulton, M.D. Price, $5. Pp. 290, with 5 illustrations. New York: Schuman's, 1944.

François Magendie was born in 1783 and lived through the dramatic events in France of the French Revolution and the Napoleonic Era, a course of events which had great importance in shaping his life. His father, a surgeon, was imbued with the strong liberal views of his time. He attempted to apply the principles of Rousseau to the educational development of his children. It may be that his early discipline and his freedom from restraint were transformed in later life to impulsive frankness, which often went too far in its vigorousness.

After Magendie obtained his medical degree, he wrote a scientific thesis which became the cornerstone for his future medical thinking and research. In this thesis he attacked the theories of Bichat. Bichat propounded the idea that an organism is imbued with "vital properties" and that the essence of these "vital properties" is that they are changeable and not measurable. Magendie attempted to show that "vital properties" can be measured and that the organism can be subjected to experimental methods.

One of his first researches was to experiment on animals with a poison used by natives on the tips of arrows, and he described the effects, the convulsions, the vomiting and the final death of the animal. He showed that the pharmacologic effect was mediated through the spinal cord. This, of course, is now known to be the strychnine effect. He employed many technics that are still in use today in pharmacologic and physiologic work. He used the technic of the isolated limb, the technic of crossed circulation and the technic of intravenous injection below a ligature. On the basis of work, he became known as the father of experimental pharmacology. He wrote a textbook of physiology in 1816, which was well received and contained information that he had derived from his own work. Some of the material in it, however, is curious, although undoubtedly true, such as "The more voluminous the buttocks and the more they are charged with fat, the greater will be the solidity of the sitting posture." He was the first to use rodents for nutritional experiments. He collaborated with a chemist in the discovery of emetine. His passion for experiment and his search for knowledge were so great that they frequently led him into strange pathways; for example, some curious experiments are described by him on the chemical analysis of intestinal gases of four executed prisoners who had dieted on bread, cheese and red wine.

In 1821 he wrote his famous formulary. He described a list of drugs and their effects in experimental situations and on human subjects, together with dosage and therapeutic uses. The book was three hundred pages long and was the forerunner of the more modern formularies.

Academic recognition came later to him than deserved. This was due chiefly to his propensity for developing strong opposition. As he grew older, his characteristics of outspoken frankness and of aggressiveness became more marked. When he believed that certain things were wrong, he said so openly. When he himself was attacked, he defended himself warmly and gave vigorous counterblows. As a result, no one could have a neutral attitude toward him. Either he was greatly admired and respected or he was roundly hated and feared.

Later in his life Magendie devoted his work exclusively to the central nervous system. He described decerebrate rigidity, circus movements as a result of cerebellar injury and the foramen of Magendie.

Some of his observations, however, were faulty, such as attributing vision to the fifth nerve because of the lack of blink response and stating that the function of the pineal gland was to open and close the aqueduct of Sylvius.

The famous controversy between Bell and Magendie over the discovery of the function of the anterior and posterior roots is of historical interest. This controversy agitated French and English medicine for a decade, and every once in a while there is still an eruption, with a review of the factors involved.

Magendie had a healthy skepticism, which he applied to the therapeutic procedures of his day. He scoffed at "shotgun" prescriptions, and he derided blood-letting therapy. His point of view is well illustrated by the introduction that he wrote on becoming the editor of a journal. He stated, "Nothing is more harmful to the progress of medicine than the absurd isolation which the majority of physicians use to maintain with respect to the natural sciences. . . ."

One of his most famous pupils was Claude Bernard, who succeeded him to the professorship of medicine at the College of France. Claude Bernard said that Magendie loved to assume a certain aggressiveness, particularly toward younger members of his profession. He would always contradict what they told him. He wanted the young men to persist in their points of view and ultimately to demonstrate the truth of their assertions. If the truth were so demonstrated, Magendie was always willing to listen and to accept the facts.

Magendie was married in 1830. Unfortunately, the author reveals little about his personal life and his emotional reactions of a more intimate nature. The readers of today, who are accustomed to the modern historical novel and the psychoanalytic biography, will miss anecdotes and will miss sufficient personal detail to build up a picture of Magendie as a man. However, one obtains from the book a good deal of the scene of France of the day and some smattering of a historical background.

The book is interestingly written and very readable. It is evident that a good deal of research and scholarship has gone into compiling the data.

As a historical review of the scientific life of Magen-

# INDEX TO VOLUME 54

The asterisk (*) preceding the page number indicates an original article in the Archives. Subject entries are made for all articles. Author entries are made for original articles and society transactions. Book Reviews, Obituaries and Society Transactions are indexed under these headings in their alphabetical order under the letters B, O and S, respectively.

THE ARCHIVES OF NEUROLOGY AND PSYCHIATRY is published by the American Medical Association to stimulate research in the field of diseases and disorders of the nervous system and to disseminate knowledge in this department of medicine.

Manuscripts for publication should be sent to Dr. Tracy J. Putnam, Chief Editor, 710 West One Hundred and Sixty-Eighth Street, New York 32, or to any other member of the Editorial Board. Books for review and correspondence relating to the editorial management also should be sent to Dr. Putnam. Communications regarding subscriptions, reprints and other matters should be addressed, ARCHIVES OF NEUROLOGY AND PSYCHIATRY, American Medical Association, 535 North Dearborn Street, Chicago 10.

Articles are accepted for publication on condition that they are contributed solely to the ARCHIVES OF NEUROLOGY AND PSYCHIATRY. Manuscripts must be typewritten, preferably double spaced, and the original copy should be submitted. Zinc etchings and halftones will be supplied by the Association when the original illustrations warrant reproduction and when their number is not considered excessive.

Footnotes and bibliographies (the latter are used only in exhaustive reviews of the literature) should conform to the style of the *Quarterly Cumulative Index Medicus*. This requires, in the order given: name of author, title of article and name of periodical, with volume, page, month—day of month if the journal appears weekly—and year.



The ARCHIVES OF NEUROLOGY AND PSYCHIATRY is published monthly. The annual subscription price (for two volumes) is as follows: domestic, $8.00; Canadian, $8.40; foreign, $9.50, including postage. Single copies are 85 cents, postpaid.

Checks, money orders and drafts should be made payable to the American Medical Association.

# CONTENTS