MULTIPLE DEGENERATIVE SOFTENING VERSUS MULTIPLE SCLEROSIS *

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Recent histopathologic studies of the central nervous system have brought to light a group of cases presenting peculiar lesions in the form of scattered foci of degeneration. These foci or plaques differ microscopically from the patches of multiple sclerosis, encephalomyelitis and similar conditions and may be the cause of many indefinite clinical syndromes. These probably include many cases described as degenerative encephalitis, disseminated encephalomyelitis, malignant or acute multiple sclerosis, poliomyelitis superior of Wernicke, and other conditions. Generally speaking, they do not conform, either clinically or pathologically, to any established morbid entity.

The histopathologic examination of such a case seems to justify the conclusion that we are here dealing with a disease group *sui generis* which we propose to designate as multiple degenerative softening in order to emphasize the contrast with multiple sclerosis.

CLINICAL REPORT OF A CASE (DR. BASSOE)

History.—A man, aged 28 years, was first in the Presbyterian hospital from June 8 to July 2, 1921, on account of an infection of the right middle finger for which he had been treated for three days previously. He was also found to have acute tonsillitis, catarrhal conjunctivitis and carious teeth. He complained of headache and generalized pain. At this time the reflexes were normal. The pupils and eyegrounds were normal. Vision was not taken as there was no complaint relating to it. During this stay in the hospital his weight decreased from 127 to 112 pounds.

He was readmitted ten days later, on July 12, complaining of frontal headache, failing vision, general weakness, difficulty in starting urination, spells of dizziness and ringing in the ears. Vision began to fail one week before admission. There had been no diplopia. On July 12 the blood pressure was: systolic, 92; diastolic, 64. There were 5,100,000 red cells, 8,200 white cells, and 94 per cent. hemoglobin. He could count fingers at 3 feet (91.4 cm.) with the

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right eye and read ordinary print at arm's length with the left eye. The right pupil was dilated, the left of normal width; both reacted sluggishly to light and fairly in accommodation. The neck was rather stiff. The knee, elbow and wrist reflexes were relatively increased on the left side. Touch sense was normal, pain sense slightly impaired in the left leg.

Lumbar puncture yielded a clear fluid with negative Wasserman, Ross-Jones and Lange gold tests and a cell count of 5. The Wassermann test with the blood was also negative. Heart and lungs were normal.

Examination.—July 16: The pupils were rather wide and equal. The sense of smell was preserved on both sides. A watch was heard at 5 inches (12.7 cm.) on the right, not on contact on the left. There was no definite facial palsy. The patient could not raise his head from the pillow; attempted passive flexion of the neck caused pain, but there was no resistance to rotation. Shrugging of the shoulders and arm movements were very strong, but he could not raise himself to a sitting posture without the aid of his arms. The bladder was greatly distended. Abdominal reflexes were not obtained. Elbow and knee reflexes were brisk; ankle reflexes were normal. The patient had difficulty in placing the heel on the opposite knee, more on account of weakness than ataxia. He had to be catheterized in the evening but voided the next day.

Course of Disease.—July 18: Roentgenologic examination of the head: "Definite evidence of digital impressions in the anterior portions of the skull, also suggested in the parietal and temporal regions. The anterior and posterior clinoid processes appeared to be fused. Sella very small."

July 18: Leukocytes, 20,800. The temperature since admission had varied between 97.2 and 99.4 F.; the pulse between 72 and 92; respiration, 18.

July 19: Vision: With the right eye he counted fingers at 6 feet (1.82 meters); with the left eye, at 15 feet (4.56 meters). The fields were slightly contracted. Pupillary reaction to light was sluggish, more so on the right. The media was clear and the fundi normal. No muscular paralysis was present. Spontaneous nystagmus developed on deviation of the eyes in any direction. Hearing was present in both ears. Vestibular tests could not be made on account of the patient's weak condition.

July 24: Urination was frequent and burning, and there were many leukocytes in the urine. The neck was stiff as before. The left pupil was slightly larger than the right. The grip of the left hand was weaker than that of the right hand.

July 25: The patient was more somnolent. The reflexes varied from hour to hour, particularly the knee jerks. The left pupil and palpebral fissure were larger than the right. He was somewhat irrational. Slight internal strabismus and facial palsy on the left were present.

July 27: The patient had an attack of Cheyne-Stokes breathing during which the pulse became imperceptible.

The temperature did not exceed 100 F. until July 28, when it rose quickly from 99 to 104.8 F. before death on July 30.

Diagnosis.—No definite clinical diagnosis was made. Among the conditions most seriously considered were tumor or inflammation of the hypophysis, frontal lobe abscesses and some form of encephalitis.

Clinical and Gross Necropsy Findings.—These findings were: an acute infection followed by headache, vertigo, failing vision and urinary distress with retention. The somewhat indefinite neurologic findings were: unequal, sluggish pupils, slight rigidity of the neck, inconstant reflexes which varied from hour

to hour, slight facial paralysis, strabismus and nystagmus. The course was acute and afebrile (except for terminal hyperpyrexia) and resulted in death seven weeks after the onset.

At necropsy the anatomic diagnosis by Dr. B. O. Raulston was: extensive right bronchopneumonia; acute right fibrinous pleuritis; encephalitis; edema of the meninges and brain; anemia and emaciation; moderate atheromatous changes of the aorta; fatty changes of the liver; narrowed cortices of the suprarenal glands; moderate hypertrophy of the spleen; fibrous adhesions between the spleen and the omentum, the vermiform appendix and the mesentery of the cecum; petechial hemorrhages in the gastric and duodenal mucosa, the renal pelvis and urinary bladder; acute hyperplasia and partial calcification of the tracheobronchial lymph glands; small accessory spleen.

Fig. 1.—Soft patch in the decussation of the brachia conjunctiva. Weigert-Pal stain; $\times 4$.

HISTOPATHOLOGIC EXAMINATION (DR. HASSIN)

The brain, received in 10 per cent. formaldehyd, had been cut into small pieces. Macroscopically these appeared entirely normal, there being no evidence of hemorrhage, abscess, focal softening, meningeal or ventricular change.

After embedding in celloidin and staining with various methods, distinct patches were discovered in the medulla oblongata, pons, corpora quadrigemina, nucleus dentatus cerebelli and nucleus caudatus. Figure 1 shows such a patch in the pons where it occupied the left half of the decussation of the brachia conjunctiva. It appeared pale, round and sharply defined, greatly resembling a patch of multiple sclerosis.

Histologic examination, however, revealed marked differences. Figure 2 shows such a patch stained with toluidin blue. It consisted of a mass of cellular elements of exclusively gliogenous origin (myelophages and various types of gitter cells). Under a higher power (Fig. 3) they appeared markedly vacuolated and, in specimens stained with scarlet red, were seen to be filled with fat. The areas at the margin of the patches contained large cytoplasmic glia cells with numerous ramifying processes and an eccentric nucleus, rich in chromatin. There were many blood vessels, mostly small capillaries, distended with blood and possessing somewhat thickened walls with prominent and well stained endothelium and dilated adventitial spaces packed with gitter cells. Nerve fibers,

Fig. 2.—Soft patch in the region of the nucleus dentatus cerebelli, consisting of a mass of cell bodies represented under a higher power lens in Figure 3. Within the patch and surrounding the same are numerous small vessels and capillaries infiltrated with gitter cells. Toluidin blue; $\times 40$.

fragments of myelin, Marchi globules and ganglion cells could not be found in the foci. Briefly, certain portions of the brain had been transformed into glia cells laden with lipoid substances, a phenomenon typical of secondary nerve degeneration.

Other areas were noteworthy, not so much for foci of degeneration as for the presence of a great wealth of blood vessels. Thus, the cerebral peduncles, the substantia nigra, the areas around the third and fourth ventricles and the medulla, all showed markedly infiltrated blood vessels (Fig. 4). At first glance they strikingly resembled the vascular condition seen in epidemic encephalitis; but

when stained by the methods of Alzheimer-Mann, Bielschowsky and Herxheimer, the infiltrating elements proved to be principally gutter cells (Fig. 5). While in smaller vessels (Fig. 6) and capillaries these were the only types of cell found, in the adventitial spaces of larger vessels the gutter cells were intermingled with cells resembling lymphocytes. They were, however, homogeneous in appearance, pyknotic, without chromatin or cytoplasm. Cells indefinitely resembling plasma cells were also present but less common. In other words, while neither plasma cells nor lymphocytes could be recognized with certainty, their presence could not be excluded.

Fig. 3.—Same as Figure 2. Myelophages (large vacuolated bodies) and gutter cells. Use hand lens. Toluidin blue; $\times 490$.

Some blood vessels and capillaries appeared quite normal, that is to say, without perivascular infiltrations, while in other rare instances there were indications of young and new-formed capillaries.

The ganglion cells, in the neighborhood of the foci, were more or less changed. The majority contained pale, chromatin-poor nuclei (as if undergoing dissolution or karyolysis) and were provided with thick, tortuous, densely stained processes. Some cell bodies were somewhat swollen, or broken up and invaded by glia cells (neuronophagia). Others were distinctly vacuolated or sclerosed and shrunken with flattened nucleus, while the majority were packed with fat. In other words, karyolysis, neuronophagia and fatty cell degeneration were the prominent phenomena in the areas of the brain containing the foci of degenerative softening.

Equally pronounced were the changes in the basal ganglions (optic thalamus and nucleus lenticularis), the subcortical white substance, the cerebral cortex, cerebellum and especially the optic chiasm. These regions contained no patches but exhibited instead, especially in the neighborhood of blood vessels, numerous foci or clusters of glia nuclei (Fig. 7). The majority were of large size, rich in chromatin, and for the most part had a generous amount of cytoplasm. On the other hand, some glia nuclei, though somewhat large in size, were rather poor in chromatin and appeared pale and quite devoid of cytoplasm. The cytoplasmic glia cells frequently merged to form rosettes (Fig 8). These were quite frequent around or within the fat laden ganglion cells (Fig. 8).

Fig. 4.—The region of the cerebral peduncles. Marked infiltration of blood vessels and capillaries resembling that seen in lethargic encephalitis. Some of the infiltration cells are reproduced in Figures 5 and 6. Use lens. Toluidin blue; $\times 70$.

An interesting feature was the presence of rod cells (Stäbchenzellen) in the form of curved, sausage-like cell bodies supplied at their poles with slender processes. They were found not only in the cortex, but also in the subcortical areas and in the basal ganglions (Fig. 8). These regions were richly supplied with blood vessels, mostly capillaries, having lipoids in their perivascular spaces, but without other pathologic changes (thrombi, endarteritis, hyaline degeneration).

The nerve cells of the cortex and the basal ganglions showed changes which were somewhat similar to those already outlined. Especially noteworthy were accumulations of fat in the cell bodies (Fig. 9) and satellitosis in the form of rosette formation. Such cell changes involved every lobe of the brain, as well as every layer, though the deeper cortical strata were particularly affected.

Fatlike substances were also present in the glia cells and the capillary walls, and sections stained with scarlet red presented appearances characteristic of parenchymatous degeneration, well shown in Figure 10.

Lipoids were equally common in the pia-arachnoid all over the cortex and were mixed with a great number of lymphocytes, polyblasts, fibroblasts, and

Fig. 5.—Nucleus caudatus: large vein infiltrated with fat granule cells—black stained cell bodies in the perivascular space, *p*, *p*, *p*. Herxheimer scarlet red; $\times 150$.

mesothelial cells. All these elements were scattered within the distended meshes of the subarachnoid space and the capsule of the pituitary body. The choroid plexus likewise showed drops or droplets of fatlike substances, especially within the tuft cells.

Only the upper portion of the cervical region of the spinal cord was available for study. It showed no signs of secondary degeneration. The changes were similar to those found in the cortex: absence of large degenerative foci, presence of foci of glia nuclei, ganglion cell degeneration and absence of definite inflammatory phenomena.

The microscopic examination of the viscera and the pituitary body revealed no findings of special interest.

SUMMARY OF THE PATHOLOGIC FINDINGS AND DISCUSSION

The pathologic findings were:

1. Foci of degeneration in the midbrain, medulla and to a less extent in the nucleus caudatus.
2. Diffuse degeneration of the cortex, basal ganglions and the available portion of the spinal cord (cervical region).
3. Definite widespread gutter cell infiltration of the blood vessels, especially the capillaries, of the midbrain, basal ganglions and medulla.

Fig. 6.—Optic chiasm: small blood vessel with numerous gutter cells in the distended meshes of the adventitial space. Bielschowsky stain; $\times 275$.

4. Absence of inflammatory phenomena as well as of secondary degeneration in the spinal cord.
5. Reactive phenomena and presence of lipoids in the subarachnoid space and the choroid plexus.

Of the features described, the most outstanding were the patches of degeneration. As noted, grossly they resembled those of multiple sclerosis, but microscopically they differed greatly. Thus, nerve fibers, glia fibers and Marchi globules were entirely lacking, and the changes peculiar to the various stages of the evolution of a patch of multiple sclerosis were absent. The resemblance to the so-called second stage

of such a patch, pointed out in a previous article,¹ is certainly superficial. For even in this stage of multiple sclerosis there are present, not only gitter cells and similar structures, but also nerve fibers, either well preserved, or in an early stage of degeneration. The foci in the case here described were entirely devoid of nerve structures and in this respect resembled foci of ischemic softening. They differed from these, however, in that the general architecture of the component elements was preserved as it is not in ischemic foci of softening such as those caused by thrombosis. In the latter the parenchyma is entirely broken up.

Fig. 7.—Motor area: Clusters or foci of glia nuclei around a large blood vessel. Toluidin blue; $\times 560$.

Under the microscope the field is strewn with fragmented nerve fibers, with immense numbers of myelophages and gitter cells, many of which are crowded densely around or within the adventitial spaces of floating blood vessels. In short, the parenchyma is liquefied. The patches in this case did not show liquefaction. They were comparatively solid though much less firm than patches containing neuroglia or connective tissue. Compared with the latter, they were essentially soft, and it is in this sense that the term "softening" has been used.

1. Hassin, G. B.: Studies in the Pathogenesis of Multiple Sclerosis, *Arch. Neurol. & Psychiat.* **7**:589 (May) 1922.

In some respects they resemble the patches described by Williamson^{1a} in a case of "early disseminated sclerosis."

The patient, a young man, 23 years old, complained of paresthesias in the hands and toes followed by a successive paralysis of the upper and lower extremities. The tendon reflexes were exaggerated, with bilateral foot clonus, while the skin reflexes were absent. There was intention tremor in the hands, scanning speech and nystagmus on looking to the right; the mentality was dull. Death occurred a year after

Fig. 8.—Optic thalamus: In the center accumulation of glia cells forming a rosette; *Ga*, ganglion cell invaded by glia cells (neuronophagia); *S*, Stäbchenzelle (rod cells). Use hand lens. Toluidin blue; $\times 560$.

the onset of the first symptoms. Necropsy revealed "soft roundish grayish-yellow gelatinous semitransparent patches" in the frontal lobe, in the center of the white substance of the left occipital and right temporosphenoidal lobes. In addition, there were found a number of "firm" patches in the white matter of the cerebral hemispheres, spinal cord, crus, pons and medulla. These consisted of dense neuroglia fibers, but showed no nerve fibers. The soft patches likewise were

^{1a}. Williamson, R. T.: The Early Pathologic Changes in Disseminated Sclerosis, *The Medical Chronicle* **19**:373 (March) 1894.

devoid of nerve fibers and consisted of numerous "fat-granular bodies," white and red blood cells, "scattered neuroglia" fibers and glia cells and numerous dilated vessels infiltrated with "round" cells. From Williamson's description of the "soft" patches one may gather that they were not typical of anything seen in multiple sclerosis and that in some features they resembled the patches of our case.

The latter much more closely resembles the cases of Oppenheim and Henneberg,² Kramer and Henneberg,³ Redlich,⁴ Schultze,⁵ a case described by one of us⁶ and partly the case of Alzheimer.⁷

Oppenheim and Henneberg's patient was a man, 39 years old, with a history of trauma (contusion of the back). The clinical symptoms were: Korsakoff's syndrome, slight optic neuritis, hypotonia, loss of tendon and abdominal reflexes, bilateral Babinski sign (in spite of the paralysis being flaccid), bulbar symptoms (dysarthria, dysphagia, chewing troubles), facial nerve paralysis and urinary disturbances. The remarkable feature was the variation of the reflexes, as in our case, and the hypotonia. Oppenheim concluded that the case was either acute multiple sclerosis or disseminated encephalomyelitis.

The histopathologic examination by Henneberg showed foci of softening in the corpus callosum, the adjacent hemispheres and cingulum. In the "distal portion of the pons and medulla" there was a large focus which microscopically looked like an "infiltrative encephalitis." The cerebral foci showed no axons, but many fat granule bodies enclosed within meshes of "connective tissue," large glia nuclei and small cell infiltration of some larger blood vessels. The spinal cord exhibited diffuse degenerative and inflammatory changes. Henneberg ascribes the foci in the brain to an "inflammatory softening" probably due to stasis, while those of the pons and medulla though resembling, he says, "malignant" multiple sclerosis, are rather "indicative of acute degenerative encephalitis."

Though Henneberg's conceptions of so-called degenerative encephalitis (and degenerative or funicular myelitis) are open to criticism, his views as to the nature of the so-called degenerative (funicular) myelitis

2. Henneberg: Ueber disseminierte Encephalitis, *Neurol. Centralbl.* **36**:652, 1916. Oppenheim: *Deutsch. Ztschr. f. Nervenhe.* **52**:172, 1914 (Case 1).

3. Kramer and Henneberg: Ueber disseminierte Encephalitis, *Neurol. Centralbl.* **36**:984, 1916.

4. Redlich, E.: Ueber Encephalitis Pontis et Cerebelli, *Ztschr. f. d. gesam. Neurol. u. Psychiat. (Originalien)* **37**:1, 1917.

5. Schultze, F.: Ueber Multiple Sclerose und herdförmige Encephalitis, *Deutsch. Ztschr. f. Nervenhe.* **65**:1, 1920.

6. Hassin, G. B.: Histopathologic Findings in a Case of Superior and Inferior Poliencephalitis with Remarks on the Cerebrospinal Fluid, *Arch. Neurol. & Psychiat.* **5**:552 (May) 1921.

7. Alzheimer: Ueber eine eigenartige Erkrankung des Zentralnervensystems mit bulbären Symptomen und schmerzhaften spastischen Kramp fzuständen der Extremitäten, *Ztschr. f. d. gesam. Neurol. u. Psychiat.* **33**:45, 1916.

being by no means universally accepted, he certainly was justified in rejecting Oppenheim's diagnosis of multiple sclerosis. The cellular infiltrations which he mentions, but does not describe, might have been fat-granule bodies (gitter cells), and the process thus wholly degenerative.

Kramer-Henneberg's case concerned a woman, 43 years old, who gradually developed left hemiplegia and hemianesthesia, preceded by asthenia, paresthesias, first in the left hand and then in the entire left side of the body, and diminution of taste in the left half of the tongue. All these symptoms, except slight weakness in the left hand, cleared up.

Fig. 9.—Putamen: lipoids in the ganglion cells can be distinctly seen, especially with the help of a hand lens. Scarlet red; $\times 275$.

Three years later, the left hemiplegia and hemianesthesia returned, together with paralysis of the right sixth and seventh cranial nerves and diminution of hearing and taste on the right side. These symptoms were followed by disturbances of deglutition and speech, strabismus and diplopia. The duration of the second attack was about three months.

Necropsy revealed a focus of softening in the right hemisphere. It involved the posterior central convolution, gyrus cinguli and corpus

callosum, extending to the white substance. Another focus existed in the medulla oblongata occupying an area comprising a portion of the decussation of the pyramids, the middle of the pons, the sixth nucleus, brachia conjunctiva, mesial lemniscus and the reticular substance. Microscopically, there was no myelin, a few glia fibers and numerous gutter cells (in the medullary focus) mixed with rod cells; the vessels were infiltrated with lymphocytes which freely invaded the neighboring tissues. Henneberg is inclined to consider this case somewhat akin to malignant multiple sclerosis, but prefers to classify it as disseminated encephalomyelitis.

Fig. 10.—Cortex: lipoid substances in the ganglion cells, glia nuclei and around capillaries. Herxheimer scarlet red; $\times 230$.

Redlich's patient, a young man, 20 years old, suddenly developed cerebellar ataxia, left ocular paralysis and nystagmus. Slight improvement was followed by paralysis of all the branches of the left, and then of the right, seventh nerve, ataxia in the right leg, increased tendon reflexes with bilateral Babinski sign and slight intention tremor. The duration of the illness was about five months. At necropsy there were found large foci of softening in both cerebellar hemispheres, extending through the posterior corpora quadrigemina into the pons, red nucleus

and the decussation of the pyramids. The foci of the midbrain consisted of numerous fat-granule cells, proliferated glia cells and hyperemic blood vessels infiltrated "so far as could be made out" with lymphocytes, and, possibly, with plasma-cells. Notwithstanding the predominance of degenerative phenomena, Redlich considers this case an inflammatory process; he therefore excludes multiple sclerosis and designates it "subacute interstitial or hyperplastic encephalitis of Hayem."

Schultze's patient, 43 years old, had "aphasic-dysarthric" troubles, right hemiparesis with exaggerated reflexes but without Babinski sign, disturbed sense of position in the right fingers and an uncertain gait. The condition gradually became worse and within three weeks there was complete right-sided paralysis with exaggerated reflexes and positive Babinski sign on both sides, marked disturbances of speech, deglutition and urination and mental depression. The patient had previously had two transient attacks of paralysis of the left arm, one about a year, the other about fourteen years, prior to the onset of the last illness which lasted altogether about ten weeks. Necropsy revealed numerous miliary foci in the left hemisphere (cortical and subcortical), pons and medulla, while the spinal cord appeared normal throughout. The foci contained no myelin, hardly any axons, many gitter cells and no infiltrated vessels. Neither clinically nor pathologically was the case clear to Schultze. He considered multiple sclerosis, encephalitis, "focal tissue destruction" and, as he put it, "probably an entirely new not yet described clinical entity." At any rate, he adds, it was not an inflammatory process.

In a case reported by one of us,⁶ the clinical picture was a combination of poli-encephalitis superior (ophthalmoplegia) with bulbar paralysis (poli-encephalitis inferior). Histologically, there were extensive foci of degeneration in the medulla, pons and midbrain, combined with diffuse degeneration of the cortex and basal ganglions.

Quite unique was Alzheimer's case. A woman, 27 years old, showed mental disorder (depression and impulsive crying) with disturbances of speech, deglutition and gait. A remarkable feature was the occurrence of attacks of painful tonic muscular contractions in the left arm which would set in on attempts to talk. The muscles of the entire left arm, except those of the fingers would become hard as wood and very painful. The painful spasmodic contractions then involved the right arm and the left leg, and to prevent such attacks the patient had to avoid talking. Death occurred about three years after the onset.

Necropsy revealed combined cord degeneration, symmetrical foci of degeneration in the seventh cranial nerve nuclei and nucleus ambiguus, in the globus pallidus (bilaterally), foci of glia nuclei (rosettes) and numerous "focal" changes in the subcortical white substance. Alzheimer was at a loss to classify the condition, which he says was unlike anything so far described. He was inclined to consider it as an atypical Wilson's disease.

A number of other cases are reported which most likely belong with the foregoing types, that is to say, in which the degenerative phenomena predominated. Unfortunately, the microscopic descriptions are so indefinite and inconclusive that these cases cannot be used.

Even in the cases quoted, the histopathologic studies, except those of Alzheimer, are rather superficial and confined to the foci. The remainder of the brain was either neglected altogether or studied partially. It is therefore impossible to ascertain whether the focal lesions were associated with a diffuse process observed in our case.

On the other hand, a few cases have been described in which the morbid process was diffuse only and resembled that found in the cortex and the basal ganglions in our case. Here belong the cases of Creutzfeldt,⁸ Jacob⁹ and Economo-Schilder,¹⁰ though the last one presents somewhat different aspects. The principal microscopic findings in these excellently studied cases were:

1. Ganglion cell degeneration with accumulation of lipoids.
2. Foci of glia cells with rosette formation.
3. Presence of lipoids in the perivascular spaces of the blood vessels.
4. Foci of destruction in the cortical layers.
5. Hypertrophied glia nuclei.
6. Total absence of inflammatory phenomena, with the occasional presence of rod cells (Stäbchenzellen).

While Economo and Schilder consider their case one of pseudosclerosis, Creutzfeldt and Jacob consider their own cases and that of Alzheimer as instances of a peculiar pathologic entity not previously described. Jacob even attempted to construct a separate clinical syndrome in accordance with the pathologic findings. Though it might be expected that diffuse, like focal, brain degenerations should give more or less characteristic clinical pictures, they must of necessity be exceedingly polymorphous and indefinite. Much will depend on the number of foci, their size and location. The morbid process, for instance, may principally affect either the medulla, pons and midbrain (as in our case), or the large ganglions (as in Alzheimer's case) and give corresponding more or less characteristic symptoms. In addition, the clinical picture will be influenced by the extent of the associated diffuse lesions.

8. Creutzfeldt, G.: Ueber eine eigenartige herdförmige Erkrankung des Zentralnervensystems, *Ztschr. f. d. gesam. Neurol. u. Psychiat.* **57**:1, 1920.

9. Jacob, A.: Ueber eigenartige Erkrankungen des Zentralnervensystems mit bemerkenswertem anatomischen Befund, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **64**:147, 1921; *Med. Klinik.*, 1921, No. 13 (4th case).

10. Economo, C., and Schilder, P.: Eine der Pseudosclerose nahestehende Erkrankung im Praesinium, *Ztschr. f. d. gesam. Neurol. u. Psychiat.* **55**:1, 1920.

This remarkable association of focal and diffuse degenerative lesions is analagous to phenomena observed in certain inflammatory disorders. Thus in epidemic encephalitis a focal midbrain inflammation is associated with more or less diffuse inflammatory phenomena, while in the present case a focal midbrain degeneration is associated with diffuse degenerative changes. The latter may coexist with slight inflammatory phenomena which, however, in our case, were so indefinite and so uncertain that they may be entirely disregarded. At any rate, it would be illogical to consider the case one of inflammation, in the presence of such intensive and extensive signs of degeneration. While resembling histologically such clinically well defined chronic degenerative diseases as the lenticular degeneration of Wilson, combined cord degeneration, amyotrophic lateral sclerosis, multiple sclerosis and similar essentially *chronic* states, the group under discussion comprises essentially *acute* degenerative states in which the clinical features are obscure, variable and difficult of interpretation.

It is therefore highly probable that, as noted, some indefinite clinical syndromes recorded as acute or "malignant" multiple sclerosis, degenerative encephalitis and disseminated encephalomyelitis, form a separate morbid entity.

For this the name "multiple degenerative softening" would seem to be the most suitable.

CONCLUSIONS

1. Besides a vast group of acute inflammatory brain lesions, there is an equally large group of acute degenerative brain lesions.
2. The latter present most varied and indefinite clinical syndromes variously described as acute multiple sclerosis, malignant multiple sclerosis, degenerative encephalitis, etc.
3. The inflammatory and the degenerative types resemble one another in the localization of the morbid process, some portions of the brain being affected more, others less.
4. The most conspicuous pathologic features of the acute degenerative type are soft patches which grossly resemble the firm patches of multiple sclerosis, but which microscopically have a definitely different structure.
5. The soft patches are associated with a diffuse degeneration of the brain substance.
6. In view of the specificity of the histologic features of the patches it would be proper to collect the acute degenerative states into a separate morbid group, under the name of "multiple degenerative softening."