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TUMOUR OF THE BRAIN, ASSOCIATED WITH DIFFUSE SOFTENING AND TURBID CEREBRO- SPINAL FLUID: REPORT OF A CASE.*

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THE diagnosis of cerebral disease is seldom easily accomplished especially if the course of events is swift and there are numerous unexpected complications. In a given case the choice of opinion may fluctuate between cerebral tumour, softening due to thrombosis of a vessel and even some type of inflammatory disease. Cardinal signs, which we hopefully look for, may be altogether lacking and such signs as are present may be grossly misinterpreted and wrongly evaluated. The case reported here not only illustrates these difficulties but carries considerable significance in regard to tumours of the brain and their influence on the surrounding tissues.

HISTORY OF CASE.

A farmer, age fifty-eight, came to The Mayo Clinic on March 28, 1928, because of difficulty of speech and weakness of the right hand and arm. He had been well apparently up to two weeks before, when his family had noticed that he frequently stopped in the middle of a sentence as if seeking the correct word. This had become more noticeable at the end of a week when he was scarcely able to talk; he could only mumble a word or two. He seemed, however, to understand what was said and he carried on his usual work up to three or four days previous to examination. It was then noticed that the right side of his face had become flattened and that saliva leaked out of the right corner of his mouth. He had had some difficulty in buttoning his clothes with his right hand. All his movements had become slower and initiative seemed to desert him. There was no complaint of headache or of vomiting.

The patient weighed about 195 pounds and looked as if he had done considerable hard work during his life. The peripheral arteries were obviously sclerosed, but the blood pressure was 125 systolic and 80 diastolic. Co-operation was practically absent in any form of examination requiring mental effort. He could perform very simple commands with

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his left hand but could not speak. There was flaccid paralysis of the right side, complete in the lower portion of the right side of the face and in the right arm, but slight movement still remained in the right leg. All sensory tests were impossible because of aphasia and mental hebetude. The Babinski sign was present on plantar stimulation of the right foot and all tendon reflexes were increased on the right side. The pupils reacted normally; there was not sufficient co-operation to estimate the visual fields, but examination of the fundus of the eye disclosed moderate sclerosis of the retinal arteries only. At no time was there any oedema of the optic discs. X-ray examination of the skull did not show anything abnormal, but diffuse dilatation of the aortic arch was shown. The specific gravity of 500 c.c. of urine was 1016; the reaction was acid, and albumin and sugar were absent. Microscopic examination did not show pus cells or casts. The hæmoglobin was 77 per cent. with 4,900,000 erythrocytes per c.mm., and the leucocyte count was 8,800. Later leucocyte counts did not show further increase.

He was ambulant during the first two days of his visit to the clinic but in the latter part of the second day the weakness of the right hand and arm progressed fairly rapidly, spread to the rest of that side of the body, and within twelve hours complete right hemiplegia had developed. He was sent to the hospital for further observation and care. The temperature, at first normal, rapidly climbed during the first few hours to 102°F. where it remained with minor fluctuations during the eight days he was under observation. The pulse remained about 90 during the same period. Mental dulness progressed rapidly into stupor and the patient lay inert except for periods of being roused for examination when he persisted in rubbing the left frontoparietal region as if it were the seat of severe pain. Percussion in that area caused him to grimace and groan. Repeated examination of chest and abdomen did not show anything unusual except that toward the end signs of bronchopneumonia appeared. Spinal puncture was performed on the day of admission to the hospital and the fluid was under 210 c.mm. of water pressure. It was opaque, greenish yellow and looked frankly purulent. Under the microscope it was found to be opaque from an enormous number of polymorphonuclear leucocytes. There were 1,600 of these per c.mm., also 107 small lymphocytes. The Nonne test was positive but quantitative estimation of protein was not made. There was prompt response in the fluid pressure to compression of the jugular veins. The Wassermann test was negative. A second spinal puncture the next day produced fluid similar in appearance but the polymorphonuclear leucocyte count was less, being 853. The small lymphocyte count, however, was greater, being 256, and there were 31 large lymphocytes. Smears of the two specimens of fluid were stained and examined for organisms but none was found and all the cultures made on various media remained sterile.

The original diagnosis was thrombosis of the left middle cerebral artery with cerebral softening. The cause of the thrombosis was considered to be cerebral arteriosclerosis. Discovery later of the turbid cerebrospinal fluid and its persistence noted in the second puncture on the following day suggested an unusual pathological process. Doubt was cast on the first opinion and it was hard to understand the significance of so turbid a fluid. In the attempt to clear up the diagnosis and, if possible, to relieve the patient of some of his symptoms, surgical exploration of the brain was advised.

On April 3, 1928, the skull was opened through a left subtemporal decompression which was enlarged to about 6 cm. After the dura was opened and reflected, the brain round the central and lateral fissures in the region of the decompression opening was found to be sunken and the convolutions were flattened and softened. There was no evidence of increased intracranial pressure. The meninges seemed normal to the naked eye and no inflammatory process could be seen. A diagnosis was made of cerebral softening due to thrombosis of the left middle cerebral artery, and nothing further was done beyond closing the wound in the usual manner. The stupor became more profound, and death occurred about twenty-four hours after the operation.

PATHOLOGICAL EXAMINATION.

At necropsy the entire brain was removed complete. Before it was put aside for further hardening it was examined grossly whereupon it could be readily seen that the left temporal lobe was enlarged to almost twice its normal size (fig. 1). On palpation the enlarged lobe was found to have undergone extensive softening, which had also extended over the left frontal and parietal lobes about 3 or 4 cm. in front of and behind the central fissure. This softening did not, however, extend very high on the surface of the hemisphere and did not reach its superior margin.

FIG. 1.—Base of brain showing enlargement of left temporal lobe due to tumour and softening. The relationship of the left middle cerebral artery to the tumour in the anterior pole of temporal lobe is shown.

After the brain had been hardened in 40 per cent. formaldehyde for several weeks coronal sections were made. In the anterior third of the left temporal lobe was found a small tumour about 5 cm. in diameter. It filled the tip of the temporal lobe, leaving a small margin of oedematous, softened brain substance. At one point inferiorly it reached the surface of the lobe (fig. 2). It was vascular and hæmorrhagic, of a dirty greyish-brown colour, and many necrotic areas and gelatinous cystic foci could be seen. It was friable and crumbled easily. Tracing it backward in coronal sections it apparently reached the anterior extremity of the inferior horn of the left lateral ventricle. At this point both brain and tumour had undergone hæmorrhagic softening and

FIG. 2.—A series of coronal sections cut through the brain posterior to the tip of the temporal lobe. The tumour in the left temporal lobe cannot be distinguished grossly from the area of hæmorrhagic infarction and necrosis associated with it. An area of softening may be traced posteriorly to the juncture of the inferior and posterior horns of the left lateral ventricle. The lateral ventricle is compressed on the left and dilated on the right.

the degenerated tumour and brain tissue merged into one another imperceptibly. This red softened area which surrounded the inferior horn of the left lateral ventricle was the centre of a wide zone of white softening. The boundaries of this white softened area could be traced easily both by the naked eye and by palpation. Posteriorly it extended the whole length of the temporal lobe and occupied the major portion of the lobe. Above, it extended into both parietal and frontal lobes as high as the level of the corpus callosum and medially it reached the lateral surface of the thalamus and involved the internal capsule (fig. 3). Anteriorly in the frontal lobe it did not extend further than the anterior end of the caudate nucleus and posteriorly in the parietal lobe it reached the juncture of the posterior and inferior horn of the left lateral ventricle. At the periphery the white softened area was sharply marked off from normal brain tissue by a raised edge and was mainly subcortical, but in a few places it reached the surface and involved the cortical grey substance and surface of the brain. The centre of the area of infarction was red, hæmorrhagic and necrotic and surrounded the cavity of the inferior horn of the lateral ventricle. Anteriorly it blended with the degenerating tumour. The body and inferior

FIG. 3.—Coronal section of brain about the middle of the third ventricle. An area of softening in left hemisphere is mapped out by inspection and palpation and its boundaries dotted with India ink. A peripheral zone of white softening and red hæmorrhagic necrotic centre surrounding the inferior horn of left lateral ventricle is shown. Tumour tissue cannot be found at this level of the section.

horn of the left lateral ventricle were compressed, resulting in a compensatory dilatation of the cavities on the opposite side and distortion of the outline of the brain. The left middle cerebral artery was examined carefully for thrombi but in the stem and in the larger branches none could be found. It was manifest, however, that the middle cerebral artery lying deep in the lateral fissure between the temporal and frontal lobes of the brain could easily become compressed by the tumour in the anterior portion of the temporal lobe (fig. 1). The cerebral blood vessels grossly were only moderately sclerotic and changes could not be seen in the meninges suggestive of a previous inflammation.

Blocks of tissue were taken for microscopic examination from: (1) the tumour; (2) the softened area both in the region of the inferior horn and in the peripheral margin of softening; (3) the cortex of the temporal lobe in the vicinity of the tumour and from other more remote portions of the brain including the attached meninges, and (4) the blood vessels, including the left middle cerebral and left internal carotid. The tissues so selected were stained with hæmalum and eosin, Van Gieson's stain, Cajal's gold sublimate method and Orlando's modification of Bielschowski's silver impregnation stain. Sections of the tumour were the first to be examined and they showed it to consist of rapidly growing cells. It also contained numerous areas of necrosis, hæmorrhage and degeneration. The general architecture varied according to the degree of these changes. Sections from round the inferior horn showed a necrotic hæmorrhagic mass of tissue that could not be identified because of the destruction of its component elements. Further forward cystic areas could be found and masses of cells with degeneration in the centre, forming so-called 'rosettes' and 'palisades.' In areas of cell growth as yet not degenerated a polymorphic cell-picture could be seen. The cells were of all shapes and sizes and the relative amount of the nucleus and cytoplasm varied enormously. Some cells were round and others oval; the most common cell was spindle-shaped or pyriform and with Cajal's gold sublimate method of staining it could be identified as a bipolar spongioblast. There were also multipolar cells resembling immature astrocytes. A conspicuous feature in many areas was the appearance of large multinucleated so-called giant cells. Some of these had undergone hyalin degeneration and the outline of the cell was indistinct. Many mitotic figures could be seen in all stages of formation (fig. 4). Many of the larger blood vessels of the tumour showed hyaline changes in their walls; in the smaller there was proliferation of the adventitia and intima often leading to closure of the lumen. Thrombosed vessels were therefore common and were surrounded by areas of necrosis. Many of the vessels also had ruptured and spilled their contents so that the resultant picture included many areas of hæmorrhagic necrosis. Altogether, the tumour was a rapidly growing one, composed of cells extremely varied in shape and size and containing many giant cells and mitotic figures. It was mostly necrotic and hæmorrhagic, and was a fairly typical example of a spongioblastoma multiforme (fig. 4).

FIG. 4.—Variety in shapes and sizes of cells is obvious. Multinucleated giant cell in centre of field and mitotic figure to the right and slightly above are shown. A diagnosis of spongioblastoma multiforme was made (x 700).

In the portion of the growth where it surrounded the inferior horn of the lateral ventricle it was impossible even microscopically to tell where tumour ended and necrotic brain tissue began. Tissues from this region consisted of homogeneous stroma strewn with black granules of blood pigment, many 'gitter' cells and faint shadows of degenerated glia and nerve cells. Further, posteriorly sections were taken to include the wall of the inferior horn and its ventricular surface, in areas apparently not completely degenerated and free from tumour. The ependymal lining here was completely denuded and the subependymal tissues were oedematous and contained many cells chiefly of the scavenger type. The adventitial spaces of many of the vessels were packed with 'gitter' cells which with Scharlach R stain were shown to be loaded with fat. Many polymorphonuclear leucocytes were free in the tissues, or round the blood vessels, and in a considerable number of places were gathered into relatively large dense masses almost suggesting abscess-formation. These masses were just under the surface of the ventricular wall and in a few places had reached it and had made contact with the cavity of the inferior horn. The area of white softening outside the central hæmorrhagic necrotic portion showed the usual picture of cerebral softening and it seemed to be relatively recent. The tissues were oedematous, there was a multiplication of glial cells of various shapes and sizes, and the nerve cells had become shrunken and

distorted and stained poorly. 'Gitter' cells in abundance were found free in the tissues or clustered round the blood vessels and in their adventitial spaces. At the periphery where the softened and normal areas joined there was an even greater increase in neuroglial cells, but the infarction being fairly recent fibrillar tissue had not as yet been formed. Sections of cortex covered by the meninges, taken from the area of tumour and softened brain, showed nothing more than relatively mild infiltration of the subarachnoid space with lymphocytes. There was no evidence of gross inflammation. Sections of the large blood vessels, including the internal carotid and middle cerebral arteries, showed a mild degree of arteriosclerosis.

DISCUSSION.

In this case, without appreciable warning, progressive hemiplegia, aphasia and stupor had developed and led to death within three weeks. At no time were there symptoms or signs suggesting increased intracranial pressure. It was, therefore, reasonable to assume at the beginning that the condition was progressive thrombosis of the middle cerebral artery causing a wide area of infarction of the brain. Actually this was the case but the mechanism of its production was not at first suspected. Later the turbid cerebrospinal fluid acted as a warning that the case was unusual from the standpoint of uncomplicated thrombosis in an arteriosclerotic patient. As a remote chance of saving the patient an exploratory craniotomy was carried out, and a large cerebral softening was found. However, postmortem examination revealed a small tumour in the tip of the left temporal lobe. Presumably it had not caused symptoms until by virtue of its situation it had led to compression and thrombosis of smaller branches of the left middle cerebral artery, with resultant softening of a large area of the brain. The course of events had been swift; only three weeks had elapsed from the initial symptoms until death.

The difficulties met with in differentiating cerebral tumours and cerebral softening if patients are more than fifty years of age are notorious. There is scarcely a text-book on the subject that fails to mention this problem. Many recent articles comment on the difficulty, amongst them being one by Bickel and Frommel². They found, among a group of forty patients who had died from brain tumour, six whose condition had been diagnosed as single or multiple softenings of the brain due to arteriosclerosis. In none of these patients was the possibility of tumour even suspected. To begin with, all of the patients were more than sixty years of age and three of the six were more than seventy. The course of the disease was relatively short, and it progressed by successive apoplectiform episodes with regression of symptoms between. Vague premonitory symptoms antedated the first attack and mental deterioration of a type suggesting senile dementia was the rule. None of the six patients manifested signs of increased intracranial pressure and altogether the clinical picture was typical of single or multiple cerebral thrombosis and softening in

elderly patients. One patient, a man, age seventy-four years, markedly arteriosclerotic, had during a period of four weeks suffered from failure of memory, frequent slight attacks of unconsciousness and a tendency to fall asleep easily. During the last week of his illness he had an apoplectic attack with unconsciousness, leaving him with a flaccid right hemiplegia. He died in a few days from terminal bronchopneumonia. The clinical diagnosis was cerebral softening from progressive thrombosis of the left middle cerebral artery. Necropsy showed that he had a glioma of the left frontal area. In discussing a possible explanation for the mistaken diagnosis, Bickel and Frommel drew attention to the fact that all six patients were elderly and arteriosclerotic. The tumours were subcortical, deep, and in the majority of instances occupied silent areas of the brain. Cerebral vessels afflicted with arteriosclerosis tolerated any increase in intracranial pressure poorly. Cerebral thrombosis, therefore, was the rule before the tumour grew large enough to produce clinical signs of increased intracranial pressure. Accordingly, the clinical manifestations of these cerebral tumours in senile arteriosclerotic patients were simply those of cerebral thrombosis and softening. Possibly, had this not occurred, leading to death after one or more episodes, the usual signs of cerebral tumour might have appeared later. Actually the six patients died before any suspicion was aroused of the presence of a tumour of the brain which was masked during life by symptoms of cerebral arteriosclerosis and encephalomalacia.

The same problem, but in relation to younger patients, is described by Riley and Elsberg¹⁰ and emphasis is laid on the large areas of softening occasionally associated with infiltrating cerebral tumours. They describe three groups of cases. In the first group the symptoms were due to cerebral vascular degeneration alone, in the second group to infiltrating cerebral neoplasms uncomplicated by vascular changes, and in the third group to infiltrating cerebral tumours associated with large areas of cerebral degeneration round the tumour. Considerable similarity may exist in the clinical picture of each group, and to distinguish one from the other may be difficult. The third group mainly concerns the present discussion and in connection with it they report the cases of four patients between the ages of thirty-six and forty-seven years. In all of the cases the symptoms and course of the disease in its early stages were like those of a progressive cerebral vascular lesion. Surgical exploration nevertheless was carried out in all four because of a reasonable uncertainty about the diagnosis. In two the surgeon was deceived by the extensive area of softening, and he doubted the existence of anything but vascular disease. Later, signs of increased intracranial pressure appeared and caused a change of opinion. Necropsy in both these cases showed deep-seated infiltrating tumours. In the third case a diagnosis was made both clinically and at operation of softening due primarily to vascular disease. Death occurred before signs of increased intracranial pressure appeared, but

necropsy showed a tumour. In the fourth case the true state of affairs was recognized both clinically and at operation and later proved by necropsy. Riley and Elsberg assume that the absence of signs of increased intracranial pressure early in the disease is due to the softening making room for the growing tumour. The large areas of softening associated with these infiltrating tumours were thought to be due to compression of some large vessel by the tumour. Three of the tumours were gliomas (type unspecified), while one was a spongioblastoma.

Another factor to be taken into consideration in regard to the problem of associated tumour and softening, is the histological character of the growth. In the case recorded here the tumour was a spongioblastoma multiforme. As described by Globus and Strauss⁴ this is the one type of tumour frequently associated with an acute, almost precipitate onset of symptoms, an extremely rapid development of clinical manifestations and an unusually brief clinical course terminating in death. Bailey and Cushing² also refer to this rapid progress and estimate a grave prognosis in cases in which such a tumour can be diagnosed at operation. They also point out the relative frequency with which it appears in middle life. It is predominantly represented in the fifth decade when hypertension and arteriosclerosis appear to confuse both the picture and the clinician. In a later article Globus and Strauss⁵ emphasize this difficulty. Among others they report the case of a woman, age fifty-two years, who had hypertension and general arteriosclerosis. Right hemiplegia developed within the period of a week before admission to hospital. She was apathetic, resistant, confused, somewhat disoriented and emotionally unstable. The eye-grounds showed retinal arteriosclerosis and at first a diagnosis was made of cerebral arteriosclerosis with softening in the left motor area. Three weeks later, swelling of the optic disc appeared and increased to 5 diopters. Accordingly a diagnosis of tumour was made, and was confirmed later by necropsy. From the standpoint of pathology these authors, as well as Bailey and Cushing, refer to the marked hæmorrhagic necrosis and degeneration in them and the wide zone of cerebral oedema surrounding them. From what has been said before, it is possible also that the site of the tumour and the condition of the cerebral vascular system have a further influence in the degree of infarction occurring in and round the tumour. In this case the rapidly growing tumour situated at the tip of the temporal lobe probably compressed the middle cerebral artery by virtue of the failure of the brain to accommodate itself to so speedy a change in volume. The occlusion of such a large vessel would tend to increase the degree of local necrosis in the tumour as well as to produce a large area of softening around it. Further, if a patient is in the latter part of the fifth decade the cerebral vessels tolerate poorly any disturbance in circulation, and thrombosis results readily. The onset and course of the disease, the clinical picture, the findings at operation and later at necropsy, may reasonably be explained by the histological character of the tumour as well as its particular situation.

The changes in the cerebrospinal fluid, which were a striking feature of the present case, are a little harder to understand ; yet parallel situations are to be found in the literature, and the microscopic findings in the brain were of considerable help in clearing up the problem. A moderate pleocytosis in the cerebrospinal fluid is occasionally found in cases of tumour of the brain and in cerebral softening. Greenfield and Carmichael⁶ state that five to ten cells per c.mm., many of which are macrophages, may occur in cerebral tumour, hæmorrhage or softening. Patten⁹ states that with encephalomalacia in the course of cerebral arteriosclerosis, pleocytosis is frequently encountered. Bickel and Frommel³ studied the serological manifestations in thirty cases of cerebral softening in arteriosclerosis and found pleocytosis in less than a third of the cases. They considered this frequency as not to exceed that found in cases of brain tumour. Babinski and Gendron¹ reported three cases in which the cerebrospinal fluid contained pleocytosis shortly after the occurrence of cerebral thrombosis, due to embolism in two and arteriosclerosis in the third case. In one case there were 450 cells per c.mm. the day after the cerebral accident had occurred. The relative proportion of the cells was 90 per cent. polymorphonuclear leucocytes, 6 per cent. mononuclear leucocytes, and 4 per cent. lymphocytes. Later punctures produced a fluid containing less cells and a preponderance of lymphocytes. Finally the cell count returned to normal. Marie and Gougerot⁷ have noticed what they describe as an aseptic meningeal reaction in recent cases of cerebral thrombosis and softening. This consists of a pleocytosis of lymphocytes, 50 to 100 per c.mm., and occurs in the early weeks following infarction of the brain.

Altogether in the literature there is little to suggest that simple thrombosis with infarction is frequently associated with anything like the changes found in the spinal fluid of the patient described here. From the standpoint of cerebral tumour, Spurling and Maddock¹¹ venture to say that here the cell count is generally low, usually under three per c.mm., but some latitude must be allowed for exceptional cases. Moersch⁸, for example, has made some observations in this connexion. In a group of 127 cases of brain tumour studied by him in which the diagnosis had been proved by operation or necropsy or both, nineteen showed an increase in the cell count in the spinal fluid. The nature of the cell count was predominantly lymphocytic, but in five cases the polymorphonuclear cells were in excess. The highest cell count occurred in the case of a tumour of the anterior portion of the corpus callosum. It involved both lateral ventricles in their anterior portion. A series of fluids taken in this case showed as high as 556 polymorphonuclear leucocytes per c.mm. and in one count 123 lymphocytes. The fluid was distinctly turbid. In a case of glioma of the frontal lobe which had invaded the lateral ventricle, there were 50 polymorphonuclear leucocytes and 36 small lymphocytes. Moersch believes that this invasion of the ventricular cavity or penetration of the ependymal lining by the tumour might be a factor in the production of the pleocytosis ;

Greenfield and Carmichael⁶ also suggest this possibility. Turning to the case recorded here, the necrotic degenerating tumour surrounded the anterior part of the inferior horn of the left lateral ventricle and, further back, softened brain tissue surrounded it on all sides, even to its origin from the body of the lateral ventricle. Microscopic study of the walls of the ventricles showed, in a few places, numerous masses of polymorphonuclear leucocytes lying just under the surface of the ventricle which was denuded of its natural barrier, the ependyma (fig. 5). It is natural to suppose that these collections of

FIG. 5.—Section of tissue taken from the wall of inferior horn of the left lateral ventricle. The ventricular surface denuded of ependymal lining is at the upper margin. Below it is œdematous brain tissue crowded with 'gitter' cells. Masses of polymorphonuclear leucocytes may be seen in the lower part of picture; on the left they approach the ventricular surface (x 100).

leucocytes represent a reaction of the tissues to the massive areas of necrosis and softening in their midst. Being so close to the ventricular cavity and not having any hindrance, contamination of the cerebrospinal fluid with these cellular products of tissue reaction was a necessary consequence. In places the masses of polymorphonuclear cells were so dense as almost to suggest an

abscess. The cerebrospinal fluid, however, was sterile, as shown by repeated failure to find organisms in it, and constant failure to grow any bacteria on culture. The findings in this case, therefore, seem to support the assumption of Greenfield and Carmichael as well as that of Moersch, that infiltrating necrotic tumours involving the walls of the ventricles and penetrating the ependymal lining may be associated with highly cellular cerebrospinal fluid. The preponderance of cells may be polymorphonuclear leucocytes and actually in great numbers.

The case reported here represents a few of the many reactions of the brain to tumours growing in its substance, and also represents the clinical picture that may possibly result. The age of the patient, the condition of the cerebral vascular system, the site of the tumour in relation to the large blood vessels and ventricular cavities, its rate of growth, and above all, its histological character, are all factors worthy of consideration in producing such an end result.

REFERENCES.

- ¹ BABINSKI, J., and GENDRON, A., "Leucocytose du liquide céphalo-rachidien au cours du ramollissement de l'écorce cérébrale," *Bull. et mém. Soc. méd. hôp. de Par.*, 1912, i, 370.
- ² BAILEY, PERCIVAL, and CUSHING, HARVEY, *A classification of the tumours of the glioma group on a histogenetic basis with a correlated study of prognosis*, Philadelphia, 1926.
- ³ BICKEL, GEORGES, and FROMMEL, EDOUARD, "Les tumeurs cérébrales à forme de ramollissement thrombotique progressif," *Rev. méd. de la Suisse*, 1924, xlv, 33.
- ⁴ GLOBUS, J. H., and STRAUSS, ISRAEL, "Spongioblastoma multiforme," *Arch. Neurol. and Psychiat.*, 1925, xiv, 138.
- ⁵ GLOBUS, J. H., and STRAUSS, ISRAEL, "Vascular lesions and tumours of the brain: difficulties in differential diagnosis," *Arch. Neurol. and Psychiat.*, 1926, xv, 568.
- ⁶ GREENFIELD, J. G., and CARMICHAEL, E. A., *The cerebrospinal fluid in clinical diagnosis*, London, 1925.
- ⁷ MARIE, PIERRE, and GOUGEROT, quoted by CHATELIN, CHARLES, "Cerebrospinal fluid," *Nelson's Loose-Leaf Medicine*, 1920, vi, 97.
- ⁸ MOERSCH, F. P., "Serology in brain tumours," *Jour. Nerv. Ment. Dis.*, 1923, lviii, 15.
- ⁹ PATTEN, C. A., "The human cerebrospinal fluid in systemic and diffuse degenerative diseases involving the nervous system," in *The human cerebrospinal fluid. An investigation by the Association for Research in Nervous and Mental Diseases*, New York, 1924, 359.
- ¹⁰ RILEY, H. A., and ELSBERG, C. A., "Differential diagnosis between cerebral degeneration, infiltrating cerebral neoplasm and infiltrating neoplasm with degeneration," *Arch. Neurol. and Psychiat.*, 1926, xv, 48.
- ¹¹ SPURLING, R. G., and MADDOCK, C. L., "The cerebrospinal fluid in tumour of the brain," *Arch. Neurol. and Psychiat.*, 1925, xiv, 54.