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THE ANCESTRY OF NEUROPATHOLOGY*

ROBERT HOOPER'S "MORBID ANATOMY OF THE HUMAN BRAIN".

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In the year 1796 an unsuccessful German actor and dramatist by the name of Alois Senefelder, more or less by accident, stumbled upon a new process for the reproduction of pictures by engraving on stone. Because the publishers of his day and place were too reluctant to accept the products of his pen, Senefelder felt impelled to be his own printer and publisher so that the world might not be deprived of the masterpieces which crowded his none-too-facile mind. To this end, he set up shop in the home of his parents and became absorbed in experimentation with acids and inks, metals and stones. It so happened one day that his mother asked him to jot down a list of the soiled clothing that was to be sent out to the wash woman, thinking no doubt that her rather impractical son would thus at least temporarily be engaged in useful effort. Since there was no paper at hand, Alois traced with greasy ink on a handy block of Solenhofen stone the various items as his mother called them out. With the list completed and subsequently copied on paper, the stone was laid aside. Later, out of curiosity, he etched the stone with acid and found to his surprise that the writing stood in bold relief and that a proof could be taken from it.

This observation led to "thousands of experiments" which finally resulted two years later in the discovery that prints could be made in color from a specially prepared but unetched stone. As designated by the discoverer himself, this process came to be known as lithography.

It was a far cry from the fine texture of a lithograph in color from black-and-white prints from the woodcuts or steel engravings of that day. It is not surprising, therefore, that the process was quickly utilized by printers to portray works of art, thus rescuing it from the drab use of printing calico to which it was first put. It was also but natural that lithography was soon adopted in the effort to portray disease processes both *in situ* and *postmortem*. Not only in Germany, but also in France and in England, the method became very popular for this purpose. It was in January 1826, just 25 years after Senefelder had taken out patents on the process in England, that one Robert Hooper, aided by the artistry of J. Stewart, Jr., J. Howship, and G. Kirkland,‡ and the technical

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† All illustrations in this article were furnished by the Department of Visual Education, College of Medical Evangelists.

‡ Perhaps because they worked in stone, those who prepared the stone squares for the work of the artist styled themselves as 'sculptors', while those who actually did the drawings with a greased crayon on the stones thus prepared appended the abbreviation "del't" (from the Latin, *delineavit*, "he drew it") to their names. This practice was adopted by Dr. Cushing in signing the drawings which he made to illustrate some of his early articles, although he dropped the final 't' in so doing.

skill of J. Stewart, Sen., and J. Wegewood, used this process of lithography to present to medical science, in color, the first atlas of neuropathology. But before we scrutinize more critically the art and the science of this unusual folio, a word about Hooper himself is in order.

"ROBERT HOOPER, MEDICAL WRITER"

So styled by one of his biographers, Dr. Hooper, the subject of our essay, saw come to full fruition the fourth of his long series of publications in the same year that Senefelder perfected his process of lithography. This small book bore the title, *The Anatomist's Vade Mecum, Containing the Anatomy, Physiology and Morbid Appearances of the Human Body.* It is worth while to point out that this book came to see the light of day 6 years before its author was graduated with the combined degree of Master of Arts and Bachelor of Medicine, and 2 years after he had entered Pembroke College, Oxford, when but twenty-five years of age. This promising young man had been born in London in 1773. Although he secured his medical degree in 1804, he had unfortunately created an unfavorable reaction in the minds of some of the conservative members of the College of Physicians (as enterprising young men are so apt to do), and he was obliged to get his degree of Doctor of Medicine from St. Andrews the following year (Dec. 16, 1805). A week later he was admitted, grudgingly or not, as a licentiate to the Royal College of Physicians. Dr. Hooper hung out his shingle on Savile Row and forthwith developed an extensive medical practice.

Though tempted by all the inducements of social life which were open to a successful physician of the early nineteenth century, Hooper did not turn aside from his primary interests in scientific medicine of that day. He continued to follow his early interest in pathology and began to collect a series of specimens which he used to illustrate his lectures to medical students. It became his ultimate purpose to prepare a series of illustrated atlases on the manifold diseases which afflicted the various organs and organ systems. He wrote:

> "When the 'Illustration of the Morbid Anatomy of the Human Brain and Its Membranes' went to press in 1826, it was the Author's intention to publish merely a series of coloured engravings, which would have embraced, when completed, representations of the most important morbid appearances to which the viscera of the human body are subject: and he intended those of the brain as a specimen of the manner in which the whole would be executed. He has since been induced to add considerably to those Illustrations of the Brain, and to form a complete account of the Morbid Anatomy of that organ: and he now announces that the volumes which will follow, will also contain the morbid anatomy of the several viscera, instead of their being mere illustrations of it by engravings."[1]

It was Hooper's effort, moreover, to make this work of value to the man dealing with disease. He added:

> "The utility of this undertaking must be apparent to everyone, when it is recollected that the object is to diffuse the knowledge of morbid structure, and enable the pathologist to distinguish organic diseases from one another, and thereby dispose them into classes, orders, genera, species, and varieties. When this is satisfactorily done, and the peculiar derangement of the functions of the living body ascertained, which arises from the peculiar

organic disease, nosology will assume a new and permanent arrangement, and the practice of physic arrive at its greatest perfection."

It was evidently Hooper's purpose to make pathology practical for the man who has to deal with diseased patients, not a science for science's sake alone. Perhaps there were those a century and a half ago as now who were interested in making Pathology the dictator, not a *diener*, of Medicine.

But Hooper's aim to create a great atlas of pathology, lithographed in color, was not to be achieved. In 1832 there appeared the second volume of the series on *The Morbid Anatomy of the Human Uterus and Its Appendages with Illustrations of the most frequent and important Organic Diseases to which those Viscera are subject.* Here the effort ends, for Hooper passed to his reward on May 6, 1835, in his sixty-third year.

To leave the subject of Hooper's writings at this point would be a mistake, for though he wrote nothing additional dealing with pathology of the nervous system, there were many other products of his pen which portray something of the versatility of the man. In all, he wrote twelve works on subjects varying as widely in interests as botany (*Observations on the Structure and Economy of Plants*, etc. (1797)), anatomy (*The Anatomist's Vade Mecum*, etc. (1798)), epidemic diseases (*Observations on the Epidemical Diseases now prevailing in London*, (1803)), pathology (his atlases on the brain and the uterus, already mentioned), and a text-book on medicine (*The Physician's Vade Mecum, containing the Symptoms, Causes, Prognosis and Treatment of Diseases* (1809), some of which went through several English and American editions. His efforts were not all original, for we find that he translated from the Latin Plenck's *Hygrology, or Chemico-Physiological Doctrine of Fluids of the Human Body* (1797), and later published an edited edition of John Quincy's popular *Lexicon Medicum* (in later editions he failed to mention the original author, a medical habit which seems to have persisted well into the twentieth century). This book continued to be popular, and a number of editions were published.* He also published atlases of the anatomical plates of the bones and muscles, and the thoracic and abdominal viscera, which were reduced from Albinus' treatise. Of lesser scientific interest, but portraying Hooper's interest in the problems of students of medicine and recent graduates therefrom, are his *London Dissector* (1804) and his *Examinations in Anatomy, Physiology, and Pharmacy* (1807) the latter of which went through four editions.

Of his professional attainments there were many (most of which are indicated in his atlas by *&c, &c, &c.*), but aside from his ultimate attainment of 'Member' in the Royal College of Physicians in London, and his appointment as physician to the St. Marylebone Infirmary, little has been written. From the income of

* The particular edition in the library of the Department of Nervous Diseases is the fourth American, which was taken from the last (6th) London edition, which appeared shortly before (1834) the death of the compiler. This dictionary is of interest in securing definitions of the terms which Hooper used in his atlas on pathologic lesions of the human brain.[2]

his practice, and that from royalties of his now many books, Hooper accumulated a sizeable fortune. He retired from his practice in 1829 at the early age of 57 and died 6 years later, in 1835. He had published no new works after the age of 60, his last efforts being directed toward his pathologic studies on the uterus. It remained for his French contemporary, Jean Cruveilhier, to accomplish what he had set out to do. But this is another story and must be left for another time.

"THE MORBID ANATOMY OF THE HUMAN BRAIN"

The atlas which bears this title was printed, first as a series of loose sheets in 1826 and then as a thin folio volume in 1828, by A. and R. Spottiswoode for the author and sold by Longman, Rees, Orme, Brown and Greene.* Without presuming to be self-exalting, the author states (in the 'Advertisment' appearing on the cover of the folio edition):

> "To the accuracy of the delineations, and the faithfulness of the colouring, the greatest attention has been given, without regard to trouble or expense. The result is so satisfactory to the Author, that he is convinced the work will not only afford those who have not had the opportunity of making exispicial dissections, or of investigating diseased parts, the means of becoming acquainted with their structure and appearances on examination, but also put them in possession of a MUSEUM, in some respects more useful than the preparations themselves."

And this description of the colored lithographs is scarcely overdrawn.

According to the author's preface, the material contained in this atlas, evidently applying to both description and illustrations, was based on the findings in a series of over 4,000 autopsies which were performed in the department of pathology (presumably of the St. Marylebone Infirmary) over a period of 30 years.

In a survey of this treatise it seems desirable to consider the classification and description as given in the text, using the more important of Hooper's plates as illustrations.

CLASSIFICATION

The author writes that, "The disease appearances which have occurred within the cavity of the cranium are produced by inflammation; tumors; collections of fluids secreted between the membranes and into the cavities of the brain, extravasated fluids; or by diseased structures and unnatural appearances not attended with tumefaction." It is upon this statement that the general classification of disease of the brain and its membranes is based. The first section of the book deals with disease processes in general, while the second is concerned with diseases of the individual parts. This first portion is scarcely more than a list of definitions, the Greek derivation of each being given in a series of footnotes. Hooper classifies all diseases as (A) inflammation, (B) tumours, (C) diseased structures, and unnatural appearances, without tumefaction, (D)

* Those who purchased these loose sheets were later given the privilege of exchanging them "without any expense" by applying at the author's residence at 21 Savile Row. Evidently the cost of production of these early sheets and the subsequent bound edition was underwritten in whole or in part by the now well-to-do Dr. Hooper.

collections of fluid between the membranes and in the cavities of the brain, and (E) extravasated fluids. Any points of interest in this part of the treatise will be considered specifically in the following sections.

The author groups the diseases on an anatomical basis, a plan which has been followed by almost every neuropathologist in the century which has followed the appearance of his book:

A. Diseases of the Membranes of the Brain.

B. Disease of the Brain, the Pineal and Pituitary Glands.

C. Diseases of the Nerves, Blood-vessels, Sinuses, &c. of the Brain.

The diseases affecting these various structures will be briefly reviewed.

FIG. 1. "Inflammation of the Dura Mater" (Plate I). Acute stage of inflammation of the internal surface of the dura (pachymeningitis interna).

DISEASES OF THE MEMBRANES OF THE BRAIN

It is quite remarkable that Hooper made certain observations on diseases of the dura mater which seem to have escaped some modern writers on this subject. For example, he accurately described both the acute and chronic phases of dural inflammation. Plate I (fig. 1) shows what is now known as pachymeningitis interna. This is indeed an unusual picture, for as Hooper himself says, "This appearance of the internal surface of the dura mater is rarely met with because the inflammation generally proceeds much further before it kills, and a quantity of serum, or of an albuminous or a puriform fluid, is secreted; and the morbid vascularity, so beautifully represented in this plate, is not discernible."

He also described in detail the findings in subdural abscess, otherwise known as subdural empyema, both in its acute and subacute states. In the former he

describes the purulent exudate as a soft pulp, "like dirty paste," lying on the internal surface of this membrane. He was uncertain whether it was secreted by the internal surface of the dura mater or external surface of the arachnoid, but concluded that it was most likely derived from the former along. In the subacute phase characterized by the organization of the pyogenic membrane, this membrane was described as "adhering loosely to the dura mater, and from which it can be easily separated" (Plate II, our fig. 2). Hooper noted the tendency for the blood vessels of the dura to dip down into this new-formed

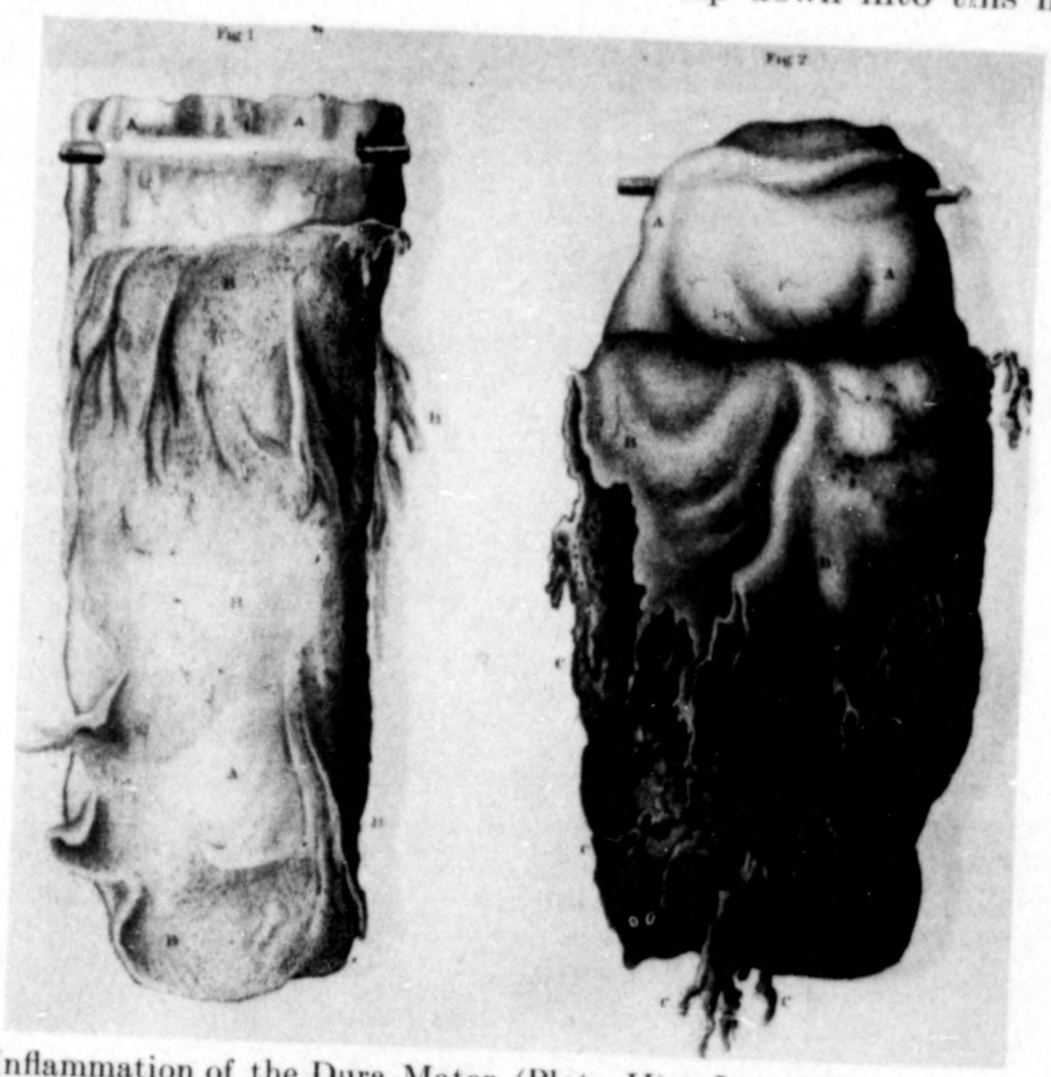

FIG. 2. "Inflammation of the Dura Mater (Plate II). Layer of granulation tissue in cases of acute subdural abscess (empyema).

membrane, an observation more recently confirmed in the completely organized external membrane of subdural hematomas.

The transparent membrane which is formed over subdural fluid accumulations was described as "perfectly organized, as delicate and diaphanous as the arachnoid in a healthy state, or the capsule of the crystalline lens of the eye", which membrane was assumed to be "the product of inflammation". This structure is well known today to pathologists interested in pathologic processes within the cranium.

Tumors of the dura form an interesting group of lesions according to Hooper. He describes scrofulous tumors, chondromatous tumors, subcartilaginous tumors, bony tumors, haematomatous tumors, cephalomatous tumors, hygroma and acephalocystis. From his illustrations (Plates VI and VII) it seems evident that his "scrofulous", "chondromatous" (whether cartilaginous or subcartilaginous), "haematomatous" and "cephalomatous" tumors are but different

varieties of meningiomas. It is very likely that his chondromatous variety is actually a degenerated angiomatous meningioma which tends to form a substance grossly indistinguishable from cartilage,[3] being rubbery in consistency, semitranslucent in appearance, and almost completely structureless histologically. It is possible, of course, that he saw a true chondroma, (which has been classified with the meningeal tumors by some), or perhaps even an osteochondroma. Hooper talks as though they were fairly common observations, which would tend to exclude this last variety which is extremely rare. Moreover, his "sub-

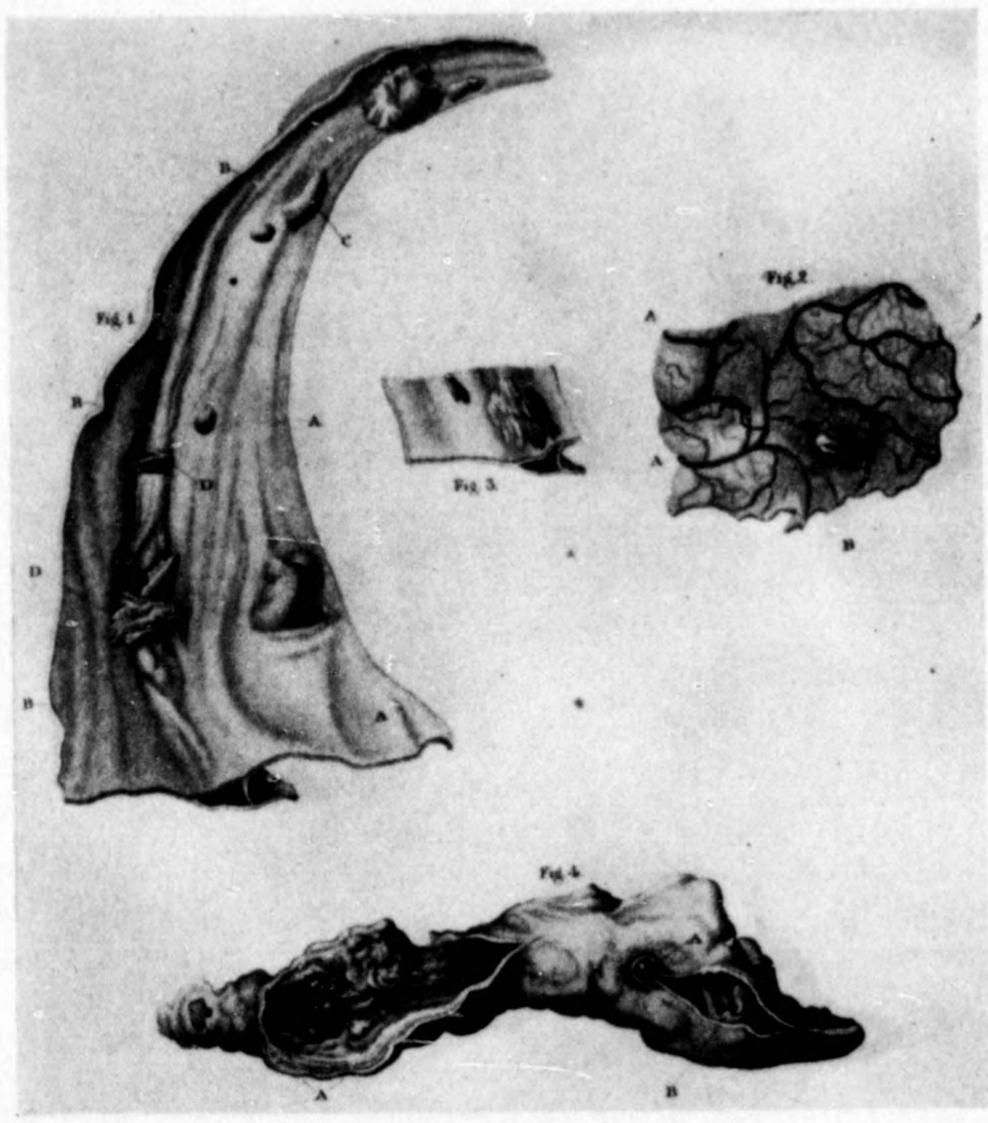

FIG. 3. "Ossification of the Dura and Pia Mater and Abscess of the Lateral Sinuses" (Plate V). The left-hand figure shows a section of the falx cerebri with typical osseous deposits in this structure. The lowermost figure shows purulent thrombosis (intrasinus abscess) of the lateral sinus.

cartilaginous variety" must be a true meningioma, for bone is described as occurring in the central portion of the example described by Mr. Watson and reported in Dr. Monro's "Morbid Anatomy of the Brain". Finally, his plate of subcartilaginous tumors (Plate VI) is as classical a picture of multiple meningiomas as one would care to see. One of this group (designated as F) is evidently an angiomatous meningioma, having a spongy, vascular structure. He saw only three examples of it, an incidence approaching the present-day experience of those studying any number of this interesting tumor.

His bony tumors of the dura are the common 'osteomas' of the falx, consisting of a "deposition of bony matter between the laminae of the dura mater". His illustration (Plate V, our fig. 3) shows several typical examples of this lesion.

What lesion is described as a meningeal *hygroma* is difficult to understand, characterized as it was as a small quantity of water between the laminae of the dura mater. His *acephalocystis* was perhaps a hydatid cyst of the dura. As is the case of the present writer, Dr. Hooper was never lucky enough to see one for himself.

As interesting lesions of the dura were also described absorption or thinning of the dura mater as the result of pressure in cases of tumor of the brain, and *unnatural colour* which was simply bile staining of this membrane in the presence of severe jaundice.

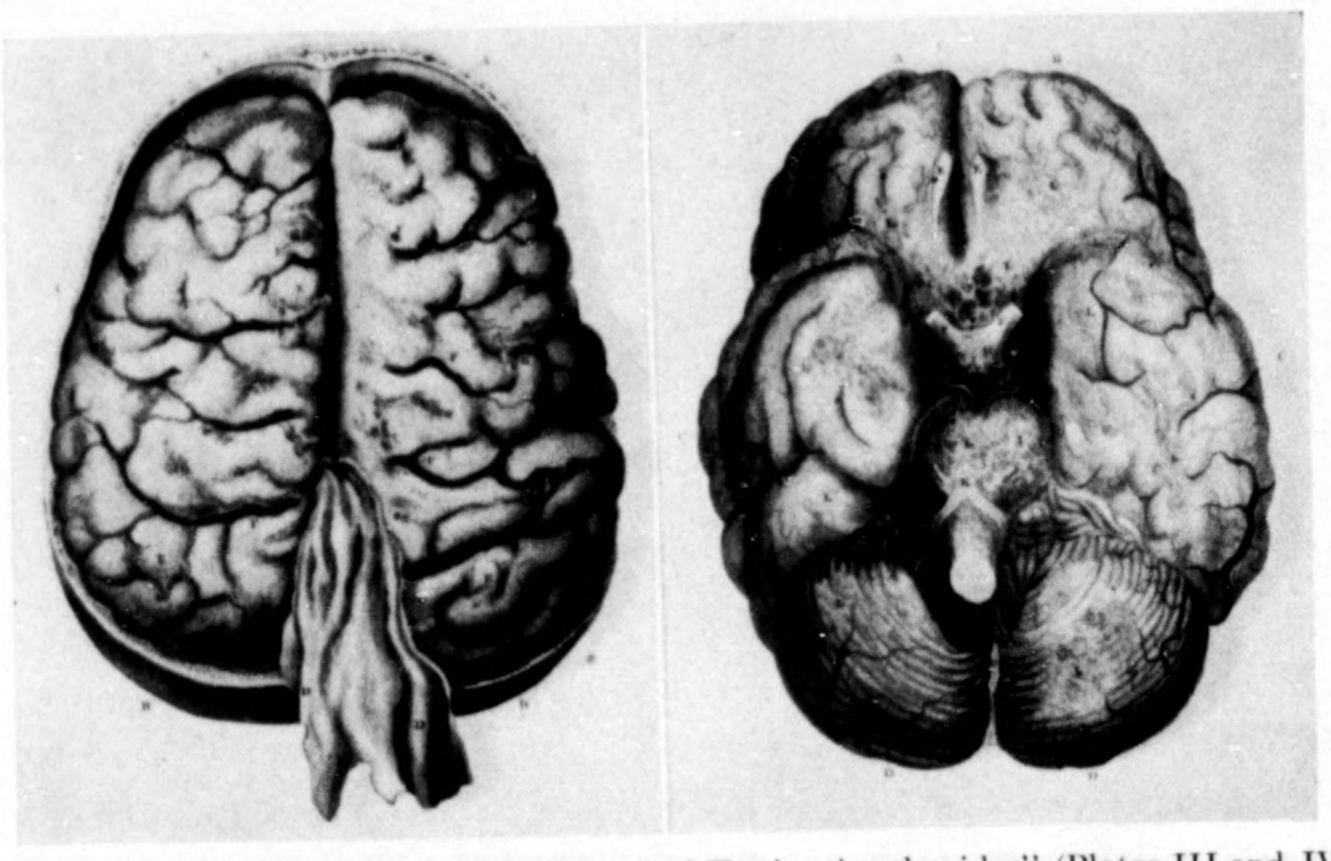

FIG. 4. "Inflammation of the Pia Mater and Tunica Arachnoides" (Plates III and IV). These lithographs show the classical findings in suppurative meningitis.

DISEASES OF THE LEPTOMENINGES

Chronic thickening of the arachnoid, such as commonly occurs in old age, was characterized as a thickness and opacity of this membrane. True suppurative inflammations of the arachnoid and pia were recognized as identical, and two excellent illustrations of purulent meningitis with dorsal and ventral views (Plates III & IV, our fig. 4) of the brain under these circumstances. The exudate was described as "patches of a yellow, albuminous, or albumino-puriform, humid substance, which occurred in small patches [geographic brain], or covered one hemisphere [unilateral meningitis sometimes seen in the otogenic form], or the greater part or whole of one lobe [localized meningitis] or covering the pons Varolii [basilar meningitis]." Our knowledge of the morbid anatomy of purulent meningitis has not gone very far beyond these original conceptions.

In his "scrofula" of the pia mater, Hooper described what are evidently multiple tuberculomas of the brain. In the specimen of this condition then

preserved in St. Bartholomew's Hospital, he described a number of "yellow tumors which seemed formed of a solid, inorganic substance, like scrofulous pus, the size of small hazel-nuts, which appear to arise from, or to be connected with, the pia mater, although they are embedded in the substance of the brain, close to the surface". It is surprising that no mention was made of tuberculous meningitis, which must have been common in that day. The small tubercles in the typical case could scarcely have escaped the sharp eyes of Hooper. But why they were not described remains a mystery.

Hooper chose to describe diseases of the choroid plexus with those of the meninges. He pointed out the occurrence of small fluid-filled cysts of the plexus, and these he called "hygromas". He also mentioned 5 kinds of cysticercus cysts of the choroid plexus.

HYDROCEPHALUS

Hydrocephalus was apparently not considered as a separate entity incident to some congenital abnormality affecting the circulation of fluid within the skull. While this condition was notably observed in infants, it seemed to be considered simply as a disturbed physiologic state. Hooper writes:

> "The ventricles of the brain are lined with a very delicate secreting membrane, and they contain the choroid plexus, through which the blood is circulated to the torcular of Herophillus. From these sources a vapour is constantly secreted, which, in children more especially, is often collected and becomes a fluid that presses and disturbs the function of the brain and soon kills. This constitutes the watery head, or hygrocephalus . . .
>
> "As the fluid collects in the ventricles, the substance of the brain is compressed. In young children, who are mostly the subjects of this accumulation, the bones of the skull are often expanded, the brain enlarged to a great size, and the head becomes distorted; but this diastasis, or separation of the bones, never takes place in adults . . .
>
> "The openings under the anterior crura of the fornix—the foramina of Monro—are enlarged, and there is, consequently, a free communication between the ventricles. The membrane which lines the ventricles is mostly thickened . . .
>
> "The quantity of fluid in hygrocephalus is very variable. In acute forms it is seldom much—perhaps a table-spoonful; from that to four and six fluid ounces. In the chronic forms, the fluid accumulated is always considerable. I have removed two pints; and cases are on record in which the quantity was much greater."

It seems clear that Hooper, with all his perspicacity, did not comprehend the mechanism of hydrocephalus. As indicated above, he believed that the fluid was derived from the ependymal lining of the ventricles and the choroid plexus, but the idea that the fluid accumulated because it was not absorbed did not occur to him. He believed, to the contrary, that when the fluid had accumulated sufficiently in the lateral ventricles, "it opens the foramina of Monro, which in such cases become more perfect foramina, and let the fluid through into the third ventricle." He apparently encountered no examples of obstructive hydrocephalus or at least failed to recognize such when present, for he states that he never found the fourth ventricle dilated.

He did evidently see a small collection of fluid in the fifth ventricle, which cavity was also found enlarged, when present, in hydrocephalus.

CEREBRAL HEMORRHAGE

Hooper describes hemorrhage into the tissues of the brain under the general term of "extravasations of fluid". While his observations are not particularly remarkable since such lesions, then as now, must have been exposed very frequently on the autopsy table, he did understand well the sequence of events which followed such extravasations. He called attention to (1) the lacerating effect of the clot on the nervous tissues, (2) the frequent rupture into the lateral ventricles, (3) the great variability in the amount of escaped blood, (4) the occasional multiplicity of the hemorrhagic foci, (5) the frequent association of grossly evident changes in the arteries, (6) the occasional occurrence of hemorrhage in the absence of such change, and (7) the occurrence of multiple small foci (purpura), although he made no suggestion as to the cause of this latter phenomenon.

Especially noteworthy were his observations as to the sequence of changes which take place in the resultant blood clot. His remarks in this regard are quoted verbatim:

"1. A state of *complete coagulation* of the blood, which is soft, and cuts like jelly.

"2. A much more *firm condition of the coagulum*; so firm that it can be turned out from the brain, when it appears like a solid body, without any tremulous movement when shook. In this state there is an appearance like a membrane or lamina around the coagulum adhering to the sides of the cavity.

"3. A *ball* sufficiently firm to require much pressure to break it. The external lamina is here more distinct. The cut surface is of a liver colour, and often of a bright bloody hue in the centre; and the outer margin is closely cemented to the brain.

"4. A *ball of brownish colour*, which cuts as firm as a portion of liver. This is closely connected by an organised and vascular tissue to the surrounding brain.

"5. A *cell* which contains *serous fluid*, sometimes of a turbid and of a dark colour, in other instances clear and pale . . .

"These several appearances have occurred in the brains of those who have died soon after, and at remote periods, from attacks of apoplexy;—from a day to one and two weeks; as many months and years; and in persons who have been under my own observation. Such alterations are, I have no doubt, caused by the attempts of nature to absorb and remove the extavasated blood: and it is worthy of remark, that in all the instances in which the persons survived the shock for more than a month, the brain which surrounded the extravasated blood was healthy, and in the others, who did not, it was pulpy."

ABSCESS OF THE BRAIN

Abscesses of the cerebral hemispheres were divided by Hooper into (1) the common abscess, (2) cellular abscess, (3) encysted abscess, and (4) scrofulous abscess. It is evident that his *common abscess* is the acute large abscess filled with thick pus covering a heavy granulation tissue membrane. It is evidently encapsulated (Hooper calls the capsule of the abscess 'its membranes'), for in these cases (he says) there is very little inflammation of the surrounding brain, or "scarcely any alteration in the texture of the brain immediately around them". Included in this group are smaller abscesses of the cerebral cortex which Hooper considered as secondary to meningitis. By the term *cellular abscess* is meant a multilocular abscess composed of multiple small collections of pus embedded in an irregular heavy stroma of connective tissue. As might be suspected, *encysted*

abscess is a heavily encapsulated lesion, evidently one of some age. The term *scrofulous abscess* is apparently not based upon the idea of a lesion with a tuberculous etiology, but rather upon the thick 'curdled pus' or a 'solid, unorganized, humid pus' which it contains.

It is regrettable that in his treatise Hooper was so concerned with the gross appearances of the various lesions of the brain that all considerations of etiology were ignored. Since most of the illustrated cases are reported as being in the 'anterior lobe' of the brain, such abscesses are very likely of frontogenous character. In one case, an abscess of the middle portion of the brain (Plate IX, our fig. 5) may have been one of the temporal lobe.

TUMORS OF THE BRAIN

Hooper distinguished between tumors of the nervous substance and those of the investing membranes, thereby unconsciously separating the gliomas from the meningiomas. This division was not sharply drawn, however, for he considered some examples of meningiomas which were deeply embedded in the nervous substances as arising from the brain itself. This group of encephalic tumors was broken down into (1) hypertrophias, (2) scrofulas, (3) chondromas, (4) haematomatous tumours, (5) cephalomas, (6) bony tumours, (7) lipomas, (8) melanomas, (9) hygromas, (10) acephalocystis, and (11) cysticercus.

It is difficult to know just what the author includes under *hypertrophias*. He evidently saw no cases of his own, but cites two cases reported by Meckel and Duncan respectively in which an infant with a large head, presumed during life to have hydrocephalus, proved simply to have hypertrophy of the brain. In each case there was increased intracranial pressure as evidenced by typical symptoms.

In his *scrofulas* he was apparently describing typical tuberculomas of the brain, as suggested both by his typical description and his direct assertion that they were 'tuberculous'. The cases of Dr. Kellie cited in this connection had multiple tubercles in the brain as well as miliary tubercles in the lungs, liver and spleen. In another case reported by Monro, a tuberculoma of the posterior fossa was found, and here the "abdominal viscera was studded with yellow-coloured tumours, and whose lungs were much diseased". In Plate XI a typical "scrofula of the cerebellum" is portrayed.

Chondromas of the brain, as of the meninges, were divided into the *perfectly cartilaginous* and the *subcartilaginous* varieties. His example of the first variety, cited from Munro, was almost certainly a nodular meningioma with a calcareous or osseous center which was deeply embedded in the brain ("a very hard tumour of the size of two fists, of a very irregular figure, having several knobs projecting from it, which consisted chiefly of cartilage, with an admixture of bony substance in its centre"). On the other hand, his subcartilaginous tumor taken from the description in Monro's "Morbid Anatomy" most certainly be a case of multiple tuberculomas of the brain, since "the lungs, liver and mesentery, were affected with tubercles of the same description".

Of particular interest is his description of *haematomatous tumours*. He writes:

"Haematoma though not common, has occurred in the substance of the brain. It is mostly fungous, arising from a small base. It generally separates the convolutions or parts about it as it enlarges, so as to appear externally upon the sur-

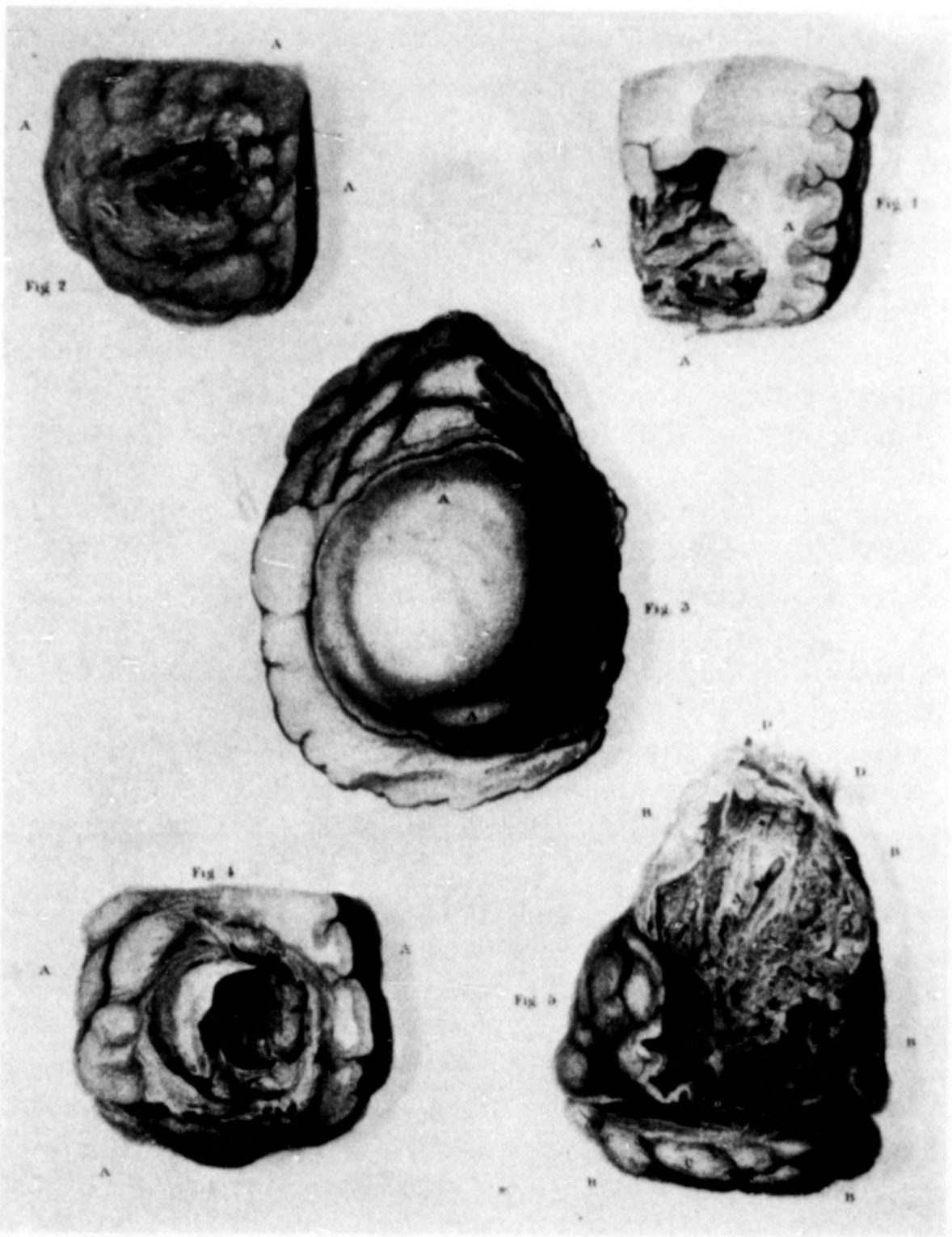

FIG. 5. "Abscess of the Brain" (Plate IX). The upper left figure shows an abscess which has ruptured to the surface of the brain with the formation of a localized subdural abscess. The upper right figure shows an acute abscess without encapsulation near the frontal pole, possibly secondary to frontal sinusitis, although Hooper says it was found in a "scrofulous subject" and was therefore probably of a "scrofulous nature." Middle figure shows an encapsulated abscess of the frontal lobe. Lower left figure shows an encapsulated (early) abscess of the frontal lobe. Lower right figure shows multiple loculations of pus in a dense stroma of connective tissue, a lesion which Hooper called a "cellular abscess."

face of the brain. See Plate X. It has a soft feel, is elastic, and covered with a shaggy membranous tissue. A humid substance adheres to the knife like cream, and the cut surface is mottled, of a whity-brown, and some parts of a

bloody colour." In the legend of Plate X (see fig. 6) he adds: "Externally, it is covered by pia mater, over which there is a very vascular, delicate membrane, which is either arachnoid altered by the disease or an adventitious membrane produced by inflammation. The fungus is irregularly lobulated. To the touch it feels soft and is somewhat elastic. It cut as firm as brain, and presented a vascular, mottled surface, of a reddish-yellow colour, with portions, here and there of a coagulated blood-like substance."

Hooper was evidently describing a malignant glioma, today called the spongioglastoma or glioblastoma multiforme, evidently a superficial lesion in a brain which was much softened by postmortem change a condition which permitted the tumor to bulge from its surface. His description of the appearance of the cut section of the tumor is also classical.

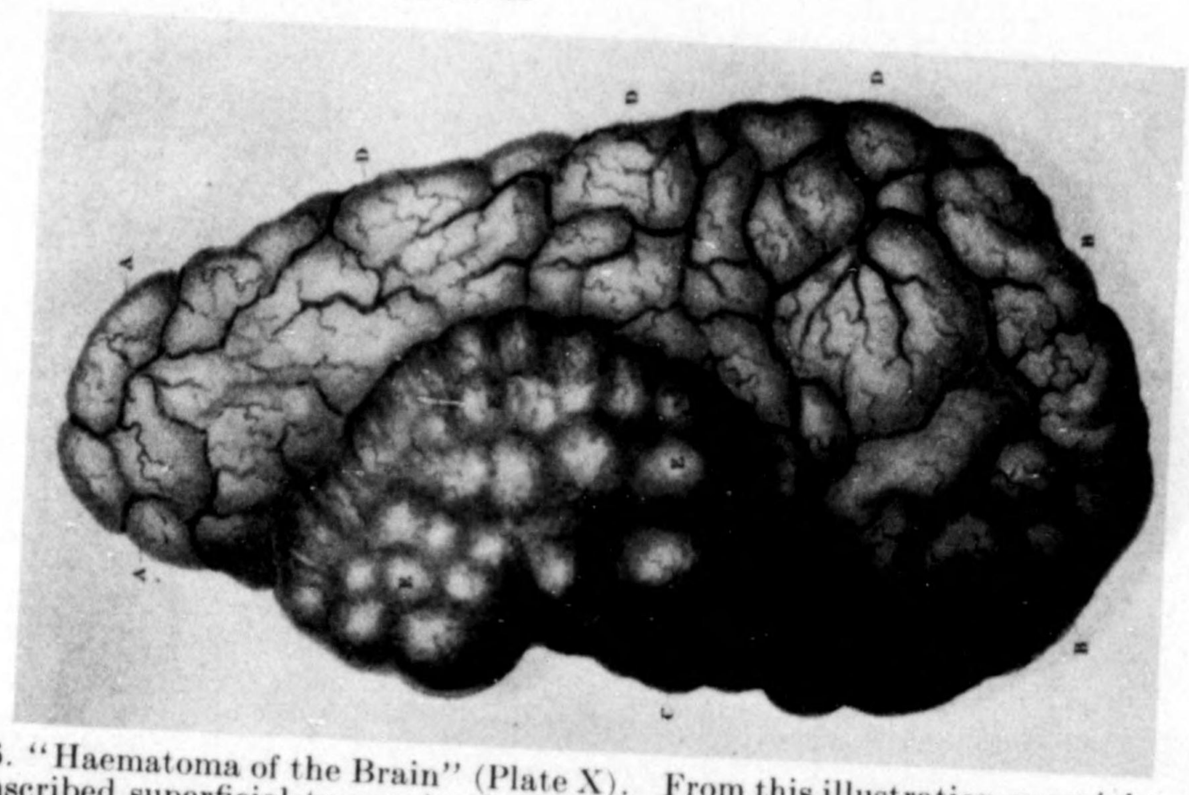

FIG. 6. "Haematoma of the Brain" (Plate X). From this illustration one might suspect a circumscribed superficial tumor (such as a meningioma), but the typical description of cross section of the lesions suggests rather that it is a malignant glioma (glioblastoma multiforme).

Hooper's *cephaloma* may also be a tubercle with a caseous center, possibly a tuberculous abscess with a heavy wall. It does not seem to be a glioma.

His collection of *bony tumors* demands special attention because of their connection with calcifications and ossifications of the brain. His own two cases may well be (1) bone formation within an abscess ("surrounded by purulent fluid") and (2) calcification or bone formation within a vascular tumor (? hemangioblastoma) of the left lobe of the cerebellum. It is also very possible that he saw examples of calcification or ossification of tuberculomas of the brain[4], for he states that "Osteoma in the substance of the brain is tuberculous, and the surface lobulated or spicular." His small calcareous particles in the brain attached to small blood vessels may also have been calcified tubercles; today, similar "particles of sand" would be called "brain sand," something not infrequently talked about by writers of textbooks but seldom actually reported.

Lipoma, or "adipose tumour of the brain", is probably but another variety of tuberculoma, but since Hooper had no personal experience with such tumors we are not clear what is meant.

Of particular interest is his reference to *melanoma* of the brain. Hooper described with modern exactness the pathology of metastatic melanoma of the brain

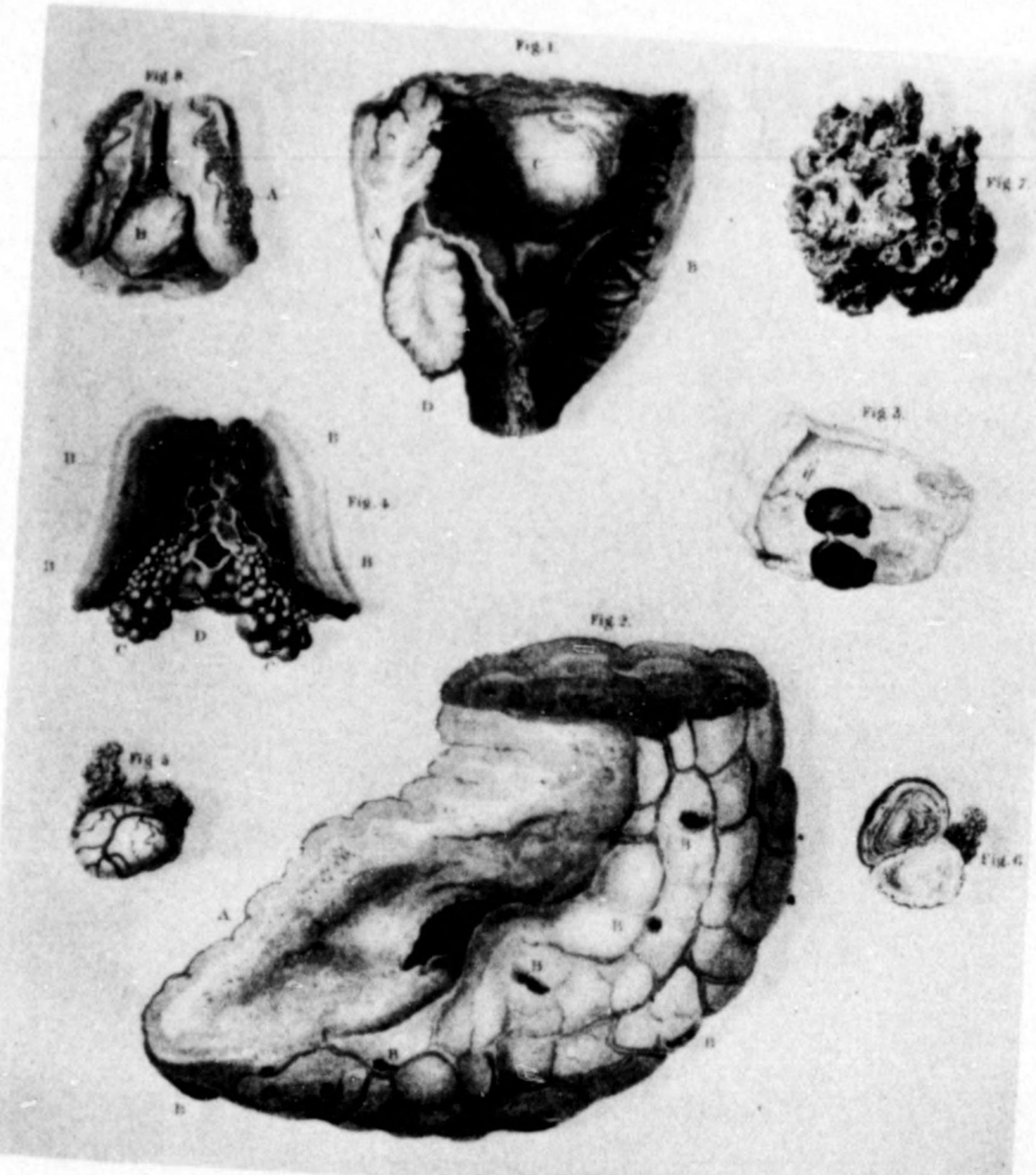

FIG. 7. "Tubercles of the Brain and Diseases of the Choroid Plexus and Pineal Gland" (Plate XII). This plate shows a group of variable lesions. The upper left figure shows a cystic pineal body. The upper middle figure presents a white tumor which bulges into the fourth ventricle from its floor, possibly a small tuberculoma. The upper right figure shows a calcareous mass which was removed from a girl of ten who had been blind for several years. It was found in the center of a collection of purulent fluid and presumably represents a central calcification of an abscess. The left middle figure indicates multiple small fluid cysts of the choroid plexuses. The right middle figure shows a small melanomatous tumor, probably metastatic, suspended from a regional vessel. The bottom central figure shows a portion of the brain with multiple melanomatous tumors. The lower left and lower right figures show the exterior and cross section of a small nodule arising from the choroid plexus, sometimes miscalled "cholesteatomas" of the plexus.

and illustrated a typical example of multiple small deeply-pigmented tumors, and describes those with this pigment. He writes:

"The black tumour is occasionally seen in the brain, and is always tuberculous [evidently in the sense of a rounded isolated mass, not a lesion due to tuberculosis]. I have found several in one brain, and in the cortical and medullary substance. These tumours are of a

jet black colour, soft, distinctly circumscribed, and closely surrounded by very healthy brain. They are found of all sizes, from that of a mustard-seed to a walnut. They are so soft as to require a very sharp knife to cut them, which they soil. They are easily taken out of the brain with forceps, and leave a clean cavity without any cyst apparent to the naked eye, and if shcok in water, they colour it black and a flocculent substance remains. See Plate XII, figures 2 and 3 [our fig. 7].

"In one instance, in which there were several of these tumours, some of them were of a blood or liver colour, and resembled haematoma; others were perfectly melanomatous; and several were of intermediate colour: a circumstance which is very much in favour of the haematoma and melanoma having an intimate connection, if they be not one and the same disease, modified by particular circumstances."

It is evident that Hooper's logic in this respect was faulty, but since his opinions were based largely on what he could see, it is not surprising that some of his ideas miscarried. Be this as it may, his description of disease can scarcely be improved upon and stands as a monument to his powers of observation.*

In his group of *hygromas*, which apparently included brain cysts of almost all varieties, Hooper recognized several varieties, (1) a simple cell, (2) an encysted tumor, (3) opaque cysts, and (4) cysts with thick walls. Hooper rightly concludes that the *simple cells*, which were filled with reddish or yellowish fluids are simply the remains of focal extravasations of blood. It is likely that his *encysted tumours* are actually gliomatous cysts, either unilocular or multilocular, the accompanying nubbin of tumor being overlooked. This is suggested particularly by his remark that the fluid content was similar in composition to blood serum. It may be that Hooper had seen large cysts of the cerebellum resulting from the presence of a small and unnoticed hemangioblastoma, but he makes no specific mention of cysts in this organ. It is very likely that his *opaque cysts* and *cysts with very thick walls* (which contained sero-albuminous, or albuminous fluid) were in actuality old abscesses of large size. His illustration (Plate XIII) would lead one to think that this was the case.

Acephalocystis and *cysticercus* of the brain were also postulated as possibilities, but Hooper himself saw no examples in his series of some four thousand autopsies.

DISEASE OF THE PINEAL AND PITUITARY GLANDS

As for the *pineal body*, Hooper described what was very likely postmortem change (extremely flaccid consistency and pulpiness), calcareous or bony deposits with a gritty or sandy feel, fibrosis (hardness) and cyst formation which are so often seen in older individuals.

The *pituitary gland* was not seen in a diseased state by Hooper, but one has reason to suspect that his two cases of enlargement of this body (twice its natural size) were actually small adenomas, for its substance had been converted into an 'obscurely fibrous texture'.

* A little more information on the historical aspects of this interesting tumor is to be found in a short review of the subject published a few years ago by Dr. Schillinger and the present writer.[5]

GENERAL DISEASED STATES OF THE BRAIN

One must be careful in reading too much into this short section of the treatise which accompanies his atlas. His *softness* or *flaccidity* was very probably post-mortem change in many instances, although secondary softening after other diseased states (such as hemorrhage or thrombosis) are evidently also included under this term. Cerebral edema is probably described in his *subanasarcous state*. *Pulpiness* evidently refers to states of advanced softening, particularly the central softenings so often seen by the neuropathologists. His *morbid firmness, hardness* or *induration* would seem to be a generalized gliosis, since it was found in aged persons and in some cases of mania (? general paresis).

Among abnormal colorations of the brain, staining of the gray matter in jaundice was observed in one of his cases.

Enlargement of the ventricles (obstructive hydrocephalus) and swelling and induration of the nervous substance in case of tumors were described under the term of *extension*. In the former condition, destruction of the septum (pel) lucidum and, in extreme cases, marked thinning of the covering cortex and white matter were included under *destruction of parts*. What remains of the brain undergoes a *condensation* and hardness, and "on a minute examination it is often found to look as if its structure were fibrous; and this appearance is sometimes better seen when a part is torn".

DISEASES OF THE NERVES, BLOOD-VESSELS, SINUSES, &c. OF THE BRAIN

In this concluding section, Hooper grouped such observations as he has made on these less prominent structures. "Nodules, like ganglia, but of a brown colour" which he observed on occasion on the nerves within the skull were very possibly neurofibromas, and one can only wish that he had portrayed such a lesion as Cruveilhier was to do *circa* a decade later.

Ossifications of the larger arteries of the brain were "extremely common", then as now, "mostly after the fiftieth year of a person's age; but I have occasionally found them as early as the thirtieth". Evidently atherosclerosis in the earlier decades is not alone the product of the rush of the twentieth century. He also observed that, "In most instances of blood found extravasated in the substance of the brain, this condition of the arteries exists, and is, most probably, the cause of the extravasation; the vessel not being able to propel the blood, which becomes stagnant, or not being able to resist the impulse from a powerful contraction of the heart." This is an old, but also new, theory of the cause of vascular rupture which leads to cerebral hemorrhage.

An *aneurysm*, evidently of the nodular type, was observed on "the left cerebral artery, close to the sella turcica, the size of a hazel-nut". Attention had already been drawn to other *aneurismas* which had their origin in a "morbid dilatation of an artery", whose coats had become thickened, subcartilaginous, or bony, a state which affected particularly the basilar and internal carotid vessels.

Postmortem thrombi of the large sinuses, "similar to that found in the cavities of the heart", were also observed. But of greater interest was the classic portrayal of a suppurative thrombosis of the lateral sinus, a lesion which today would be described as an intrasinus abscess (fig. 3).

Erosion of the inner table of the skull incident to enlargement and fibrosis of the glands of Pacchioni was also observed.

HOOPER'S CONTRIBUTIONS TO THE PATHOLOGY OF INFECTIOUS LESIONS OF THE MENINGES AND BRAIN

While, as has previously been pointed out, Hooper was one of the first to set out with the deliberate purpose to portray the gross appearance of many common and some uncommon lesions of the brain and its membranes, it is perhaps in the field of the suppurative lesions that he has been a notable pioneer. It is therefore worth while to note his position with relation to the history of these various lesions.

Of unusual value is his description of the pathology of *suppurative lesions of the dura mater*. While subdural abscess in particular had been observed in the living state as accumulations of pus beneath this membrane developing in consequence of cranial injuries, and noted in particular by Percival Pott some half-century before, the details of the lesion itself are described as seen at autopsy for the first time in his atlas. Contemporary surgeons, such as Abernethy, Guthrie, Larrey, and others, had also come to recognize this lesion as one of the indications for the application of the trepan after the frequent wounds of the brain experienced in the current wars. And yet, it is remarkable that so little attention was paid to this infectious lesion for many decades thereafter. And this is notwithstanding that the subject was reintroduced clinically by German otorhinologists of the latter years of the nineteenth century and the first years of the twentieth, who pointed out that dural infections were not uncommon after otitis media and nasal sinus infections. So much has this lesion been overlooked by contemporary neuropathologists that it is scarcely mentioned in the text-books which have been written during the past decade or two. It can therefore be pertinently pointed out that, with regard to subdural infections, Hooper was fully a century in advance of his time.

While the same can scarcely be said of *suppurative meningitis* which had evidently been recognized for what it was for several hundreds of years prior to Hooper's day, yet he did make its details unmistakably clear in a visual fashion for the first time.

Also well in advance of his time, Hooper beautifully portrayed the occurrence of infections of the dural venous sinuses. To be sure, the specific lesion which he illustrated in his colored lithograph, a frank suppuration within the lateral sinus (intrasinus abscess) was a less common type of thrombophlebitis of this channel than is usually observed as a complication of otitis media. Nevertheless a glance at his illustration indicates how much more comprehensive an impression one gains of this lesion as compared with the best photographs of our own day. In fact, the present writer knows of no better illustration of this condition at any period or in any text of the modern period.

Abscesses of the brain must have been common lesions in that day of a century ago, so that Hooper's illustrations probably were not new or startling to his well-informed contemporaries. Nevertheless, one must look far even in the prolific literature on the subject of our day to find a more well-defined visualization of

the subject than is to be found in his Plate IX (fig. 4). It must therefore be recognized that this short summary of this interesting lesion was comprehensive enough to have been a solid point of departure for any further investigation of the subject. In spite of all this, the subject was destined to lie dormant until over fifty years later, when Macewen was again to call attention to it, not so much by his description of the lesion (excellent though this proved to be), but by his remarkable facility in prolonging the life of its victims, who were almost certainly foredoomed to die.

Perhaps the greatest misfortune to contemporary medicine in Hooper's work was his failure to see the importance of associating these intracranial suppurative lesions with their primary lesion in the regional air spaces or extracranial tissues. But perhaps this was too much to ask in a period in which the importance of the problems of etiology were just beginning to be understood and in which even the exact nature of a given lesion was uncertain because of the limitations of unaided vision.

Of the granulomatous infections there is little to add. Here and there one finds suggestions that the occurrence of tubercles of the brain was recognized as a part of the generalized spread of the disease then known as scrofula. But it is doubtful that the *inflammatory* nature of the disease was appreciated, for these tubercles were commonly grouped with the tumors. Syphilis and the other more rare granulomatous diseases were completely lost in the hodge-podge of morbid flaccidities and indurations of the brain. This is also understandable, for the dawn of the bacteriological age was yet half a century in the future.

So, honor is to be tendered to one to whom honor is due. His remarkable lithographs of the outstanding lesions of the brain are delightful in their freshness and simplicity even to us today who are surfeited with the plethora of wearisome descriptions and numerous illustrations made with that new-fangled gadget known as a camera. It is of double interest to know that this latter mechanism had its conception the same year that Hooper first published his lithographed sheets (1826) when a French painter by the name of Daguerre approached a fellow countryman by the name of Niepce to see if a combination of their separate and individual experimentation with the precipitation of silver salts might be made to serve a useful purpose. This concept was to come to full fruition when Daguerrotypes came into professional use some 13 years later. But this is getting close to the modern period of the science of Neuropathology, and once more leave must be taken of the subject of its ancestry until another day.

SUMMARY

The discovery of lithography in the closing years of the eighteenth century opened the way for the more natural reproduction of pictures than was possible by the wood cuts and steel engravings of that time. Soon rescued by the artistically inclined from a rather prosaic destiny, this method was soon used to reproduce the works of the great masters. Medical science soon took the method to its own bosom, and monographs of the early nineteenth century soon came to

be illustrated with the more accurate and delineative lithographs, first in black-and-white and then in color. Robert Hooper, who had already gained a place for himself in contemporary medical life of the first quarter of that fateful century, saw in this new method an opportunity to share with his colleagues the collection of interesting specimens which he had been collecting for his private museum. By these means he hoped to place this museum within the reach of medical practitioners of this time. Even though his plans to portray the various diseased conditions of the important viscera of the body were destined to be cut short by death, his treatise and atlas of *Morbid Anatomy of the Human Brain* has become one of the notable landmarks in the ancestry of Neuropathology. While the foundation of the gross pathology of many common conditions were thus established, it is in the field of suppurative lesions of the brain in general and of the dura mater in particular that this treatise has especially created a place for itself. Perhaps it is just as well that we understand just at this time his great accomplishment, for which the introduction of the sulfonamides and such anti-biologicals as penicillin, this generation may be the last to appreciate such lesions for their full worth. In another few decades of progress the novices in medicine will probably be wondering what sort of a lesion it was that Hooper had so beautifully portrayed.

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The sections taken from blocks of the tumor proper disclosed an altogether different picture. Here four types of architecture could be made out, (1) focal areas which had a distinct fibrous appearance reminiscent of the peripheral neuromas, (2) areas in which large, typically ganglionic cells were present in abundance to the exclusion of almost all other elements (fig. 3a), (3) areas in which the great majority of cells were obviously of glial origin (fig. 3b), and (4) areas in which there was an intermingling of the large ganglionic and small glial elements. In addition, considerable portions of the sections showed more or less complete necrosis. The tumor tissue was broken up into irregular sections by connective tissue bands of varying width which formed a heavy stroma. Lymphocytes were found in varying numbers in various regions, being more abundant at the margins of the areas of degenerations.

The nature of the large cells was unmistakable. Their large size and irregular shape and multipolarity, the hyaline character of their cytoplasm, the vesicular character of their

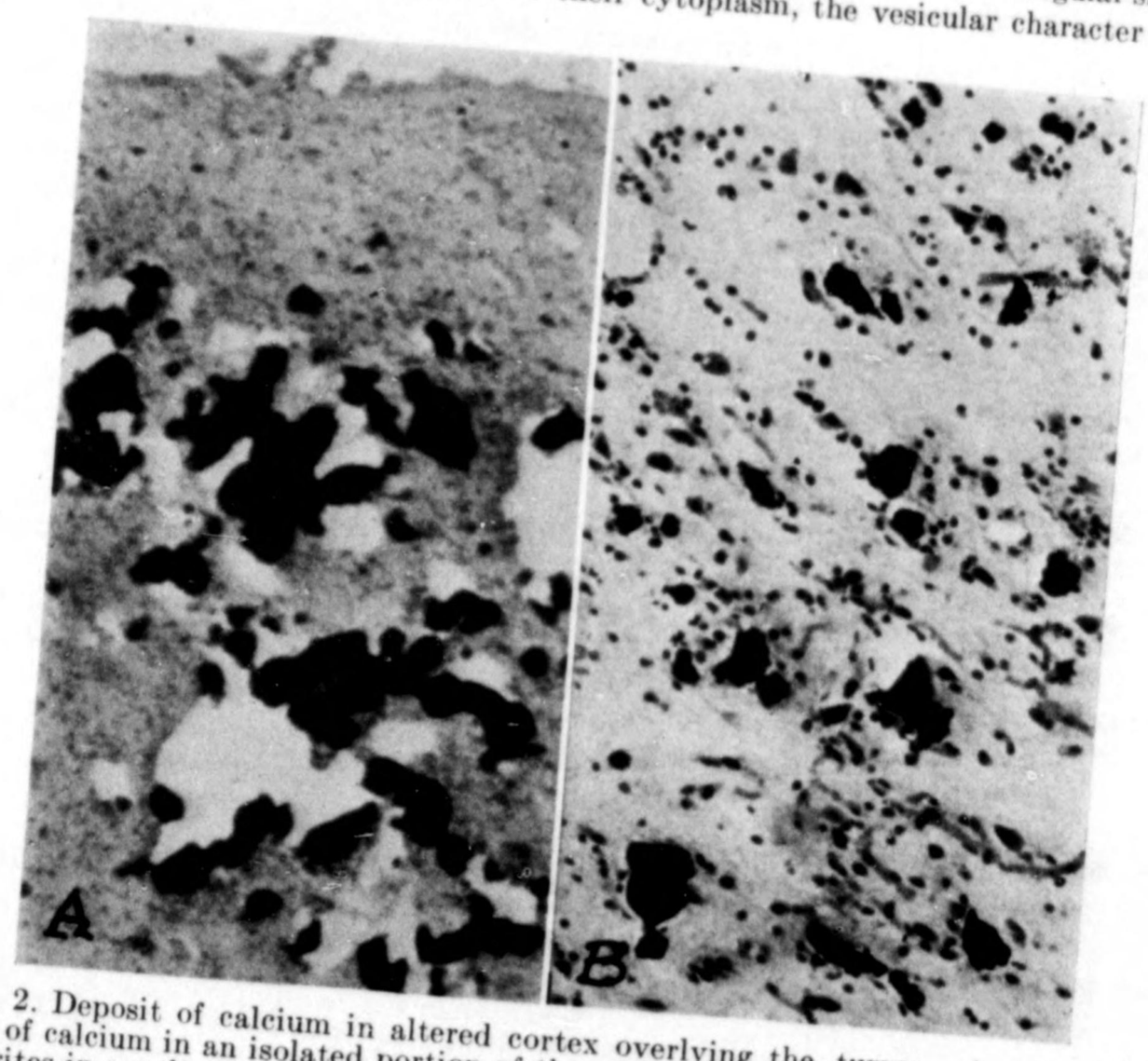

FIG. 2. Deposit of calcium in altered cortex overlying the tumor. *A*, conglomerate masses of calcium in an isolated portion of the cortex. H & E, × 37. *B*, scattered calcospherites in another region of the cortex. H & E, × 142.

one or more nuclei which contained a typical nucleolus, all indicated that these were ganglionic elements (fig. 4). As is the rule, no tigroid substance could be seen in these cells. The greater majority of these elements were evidently quite mature, although smaller unipolar and bipolar cells were also to be found. In areas of the tumor where these cells were almost exclusively present, a striking appearance was presented.

The smaller elements were obviously glial in character, as their typical nuclei indicated. In some portions of the tumor these cells constituted the majority of the cellular elements, but they were found almost everywhere in the sections studied. The cytoplasm of these cells was quite scanty and the outline of the individual cells was scarcely ever seen.

For the most part, the tumor was well vascularized, with small, medium-sized and large blood vessels being found in abundance in most portions of the tumor. There was some

euphoric, his speech was rapid, and current events did not seem to be well evaluated. No abnormal sensory, motor, or reflex changes could be detected.

Radiographs of the skull showed irregular calcification low in the region of the left frontal lobe (fig. 1). Some of the shadows in this region suggested partially calcified vascular channels. Other masses were small and irregular and quite widely distributed. There was an associated irregular hyperostosis of the adjacent inner table of the frontal bone. The floor of the anterior fossa on the left seemed eroded, and the composite shadow of the left lesser wing of the sphenoid and the orbital plate of the frontal bone had a frayed appearance suggesting erosion. The sella was oval and within normal limits, but there was a suggestion of erosion of the dorsum sellae and posterior clinoids.

Radiographs of the left shoulder showed a slightly comminuted impacted fracture of the surgical neck of the humerus extending into the greater tuberosity. The fragments were in good position and alignment.

Lumbar puncture disclosed an initial pressure of 360 mm. of water. The fluid was clear and colorless, and examination of the fluid gave normal results.

On February 15 an open reduction of the shoulder was done, and on March 18 a craniotomy was performed. A left frontal bone flap was turned down in the usual manner by one of us (P. J. V.), and, on opening the dura, the brain, except for a small strip along the posterior margin of the flap, appeared granular, was a dark red in color, and on palpation felt irregularly nodular. The frontal lobe was amputated back to the motor strip. This, however, did not remove the tumor in its entirety, as deep in the centrum beneath the motor area, tumor tissue with large calcified masses could be palpated. The day following the surgery the patient was fully awake, rational, and with no evidence of weakness of the right extremities. However, he was just as euphoric as he was prior to the operation. His recovery was uneventful, and he was discharged from the hospital on the 10th postoperative day.

Radiographs of the skull taken after surgery still showed the long linear masses of calcium present within the brain. The small irregular masses which lay in the fore part of the frontal lobe were evidently removed with the lobe at the time of operation.

The patient has been seen from time to time in the outpatient clinic and has presented no further symptoms, although recurrence of his trouble is to be expected, since a considerable portion of the tumor still remains *in situ*.

Evidently only a portion of the tissue removed at operation was forwarded to the Laboratory, for the total mass of the blocks of tissue (#46-1365) sent down was scarcely larger than a walnut. Frozen sections taken from the larger blocks were studied in connection with two of the larger masses which had been embedded in paraffin and from which sections had been taken and stained with hematoxylin and eosin. It was evident that two separate situations were to be described, one which was evidently a reaction of the cortex overlying the tumor, and the second, the nature of the glioma itself.

A study of a number of frozen sections taken from the overlying cortex disclosed the fact that there had been a profound alteration in the tissues of the cortex, which came to resemble an astrocytoma. Indeed, a study of the first sections led to this diagnosis. The lesion appeared to be a sparsely cellular growth which had replaced almost the normal architecture and cytology of the cortex, only the contour of the convolutions and the remaining leptomeninges betraying the fact that it was originally the cortical gray matter which had been so altered. The nuclei of the tumor cells were uniform in size, round or oval in shape, and filled with finely divided chromatin material which betrayed their neuroglial character. The various sections showed very little variability in the degree of cellularity of the neoplastic change from the various blocks of tissue. No degree of malignancy was thereby shown.

Here and there in the cortex could be seen small but variously-sized irregular calcospherites which represented evidently deposits of calcium in the small cortical blood vessels (fig. 2a). This change was not uniform throughout the altered cortex, for in many of the sections it was widespread (2b) while in others it was absent altogether.

Operative resection of anterior portion of the tumor. Typical ganglion cell tumor found on examination of tumor tissue. Recovery.

(Los Angeles County Hosp. No. 957-312.) G. C., a 37-year old white male, was admitted to the Neurosurgical Service of Dr. Carl W. Rand on Feb. 1, 1946. He complained of having had failing vision for the past two years, one convulsive seizure ten days prior to his admission, and a broken shoulder brought about by the convulsion. The patient stated that his vision, particularly that of his right eye, had been failing gradually over a period of at least two years. He attributed this symptom to infected sinuses, for which he had been given a 4-F rating by the Army. Ten days before admission, without warning, he developed a generalized convulsion. During this seizure his right shoulder was broken. According to his wife who witnessed the attack he was unconscious for a period of ten to twelve minutes. During the attack proper his eyes rolled up, all members were involved in the convulsive

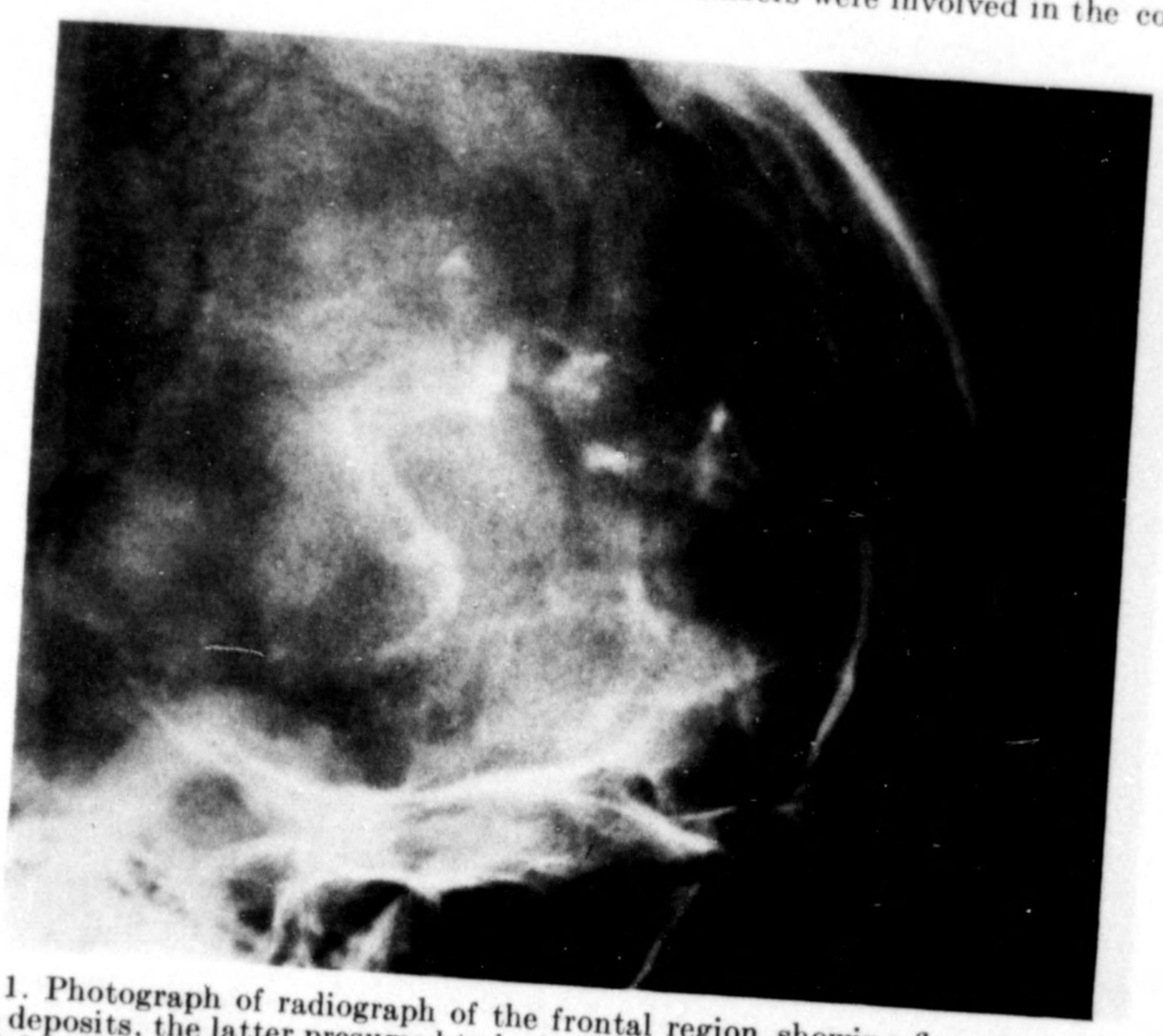

FIG. 1. Photograph of radiograph of the frontal region showing flocculent and linear calcium deposits, the latter presumed to be in the large regional blood vessels, within the frontal lobe ganglioglioma.

movements, and he bit his tongue. No localizing or lateralizing manifestations were observed. He was immediately taken to a local hospital but was discharged after nine days without a specific diagnosis having been made.

His past history was essentially negative. He had been in excellent health most of his life and, with the exception of a mild sinus infection, had had no complaints prior to his present trouble.

On the day of his admission he was alert, rational and well oriented. He was, however, very talkative and somewhat euphoric. He appeared to be in robust health and in no distress except for the discomfort of having his arm in traction. His general physical examination was entirely negative. The day following his admission a complete neurological examination was done. Although he was still alert and oriented, he seemed to be even more

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CALCIFICATION IN GANGLION CELL TUMORS OF THE BRAIN*

REVIEW OF THE LITERATURE AND REPORT OF A SURGICALLY VERIFIED CASE

PHILIP J. VOGEL, M.D., AND CYRIL B. COURVILLE, M.D.

The deposit of calcium salts as a manifestation of some slow physicochemical change taking place in intracranial tumors has long been recognized. In addition to whatever interest this process may have to those who delve into the chemical processes leading to the occurrence of calcospherites in tumor tissue, it is of much more practical importance in the localization of the enveloping tumor by the visualization of such deposits in radiographs of the skull. If these deposits are sufficiently large to avoid being "burned out" by the x-rays, and if the film is sufficiently clear, they betray very definitely the position of the growth. More than this, the presence of calcium salts also suggests that the tumor is essentially benigh and slow-growing.

When calcium is laid down in any considerable amount, so that shadows are apparent on the radiographs as being well within the substance of the brain, the chances are that the causative lesion is a glioma[1], although this is not necessarily the case. In tumors of the glioma group calcification may occur in the form of multiple particles scattered throughout the tumor, as a dense central mass, or in some instances as fused calcospherites which are condensed in the walls of the larger blood vessels, giving rise to a pattern in the x-ray film which is reminiscent of an angiomatous lesion.

It was pointed out some years ago by one of us (C. B. C.)[2] that gangliogliomas—tumors of the glioma group which were composed of dedifferentiated ganglion cells and glia cells—at times contained calcareous particles, or that such particles were found in the brain tissue at the margin of the growth. It is the purpose of the present contribution to show that this is not only the case, but that calcium may also be deposited in the walls of the larger blood vessels coursing through the tumor, giving the calcareous pattern which resembles that sometimes seen in angiomatous malformations of the brain. In support of this thesis an interesting case showing this development is to be presented. A preliminary survey of the occurrence of calcium deposit in ganglion cell tumors as reported in the literature is, however, first in order.

CALCIFICATION IN REPORTED CASES OF GANGLIOGLIOMA

While it is possible that the occurrence of calcareous salts may have been overlooked or failed to be mentioned in some of the cases of ganglion cell tumors of the brain reported to date, in the great majority of instances the details of the histologic findings have been quite painstakingly reported. This is especially true of most of the earlier cases, and on this basis it may be presumed that a fairly ac-

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Operative resection of anterior portion of the tumor. Typical ganglion cell tumor found on examination of tumor tissue. Recovery.

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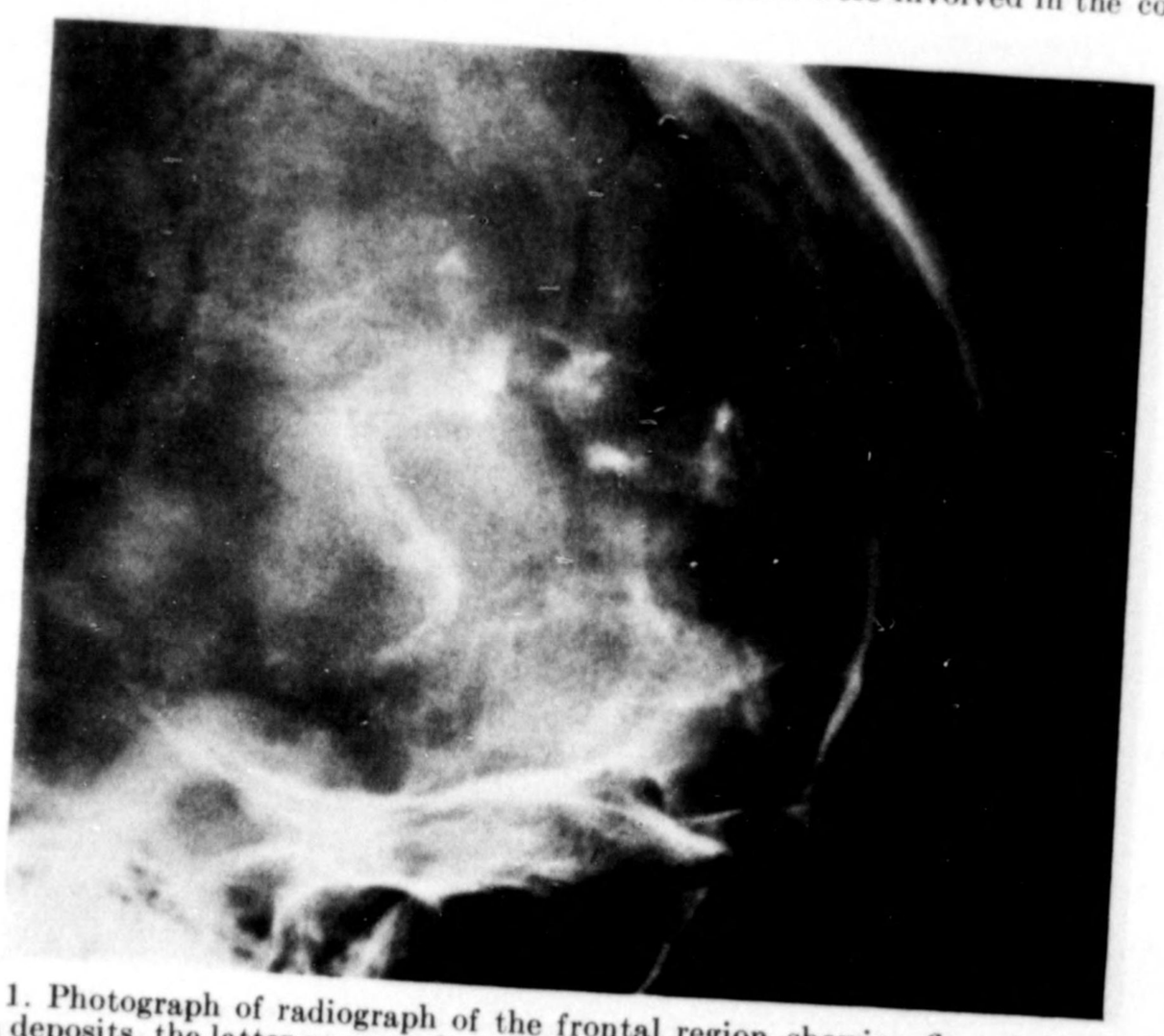

FIG. 1. Photograph of radiograph of the frontal region showing flocculent and linear calcium deposits, the latter presumed to be in the large regional blood vessels, within the frontal lobe ganglioglioma.

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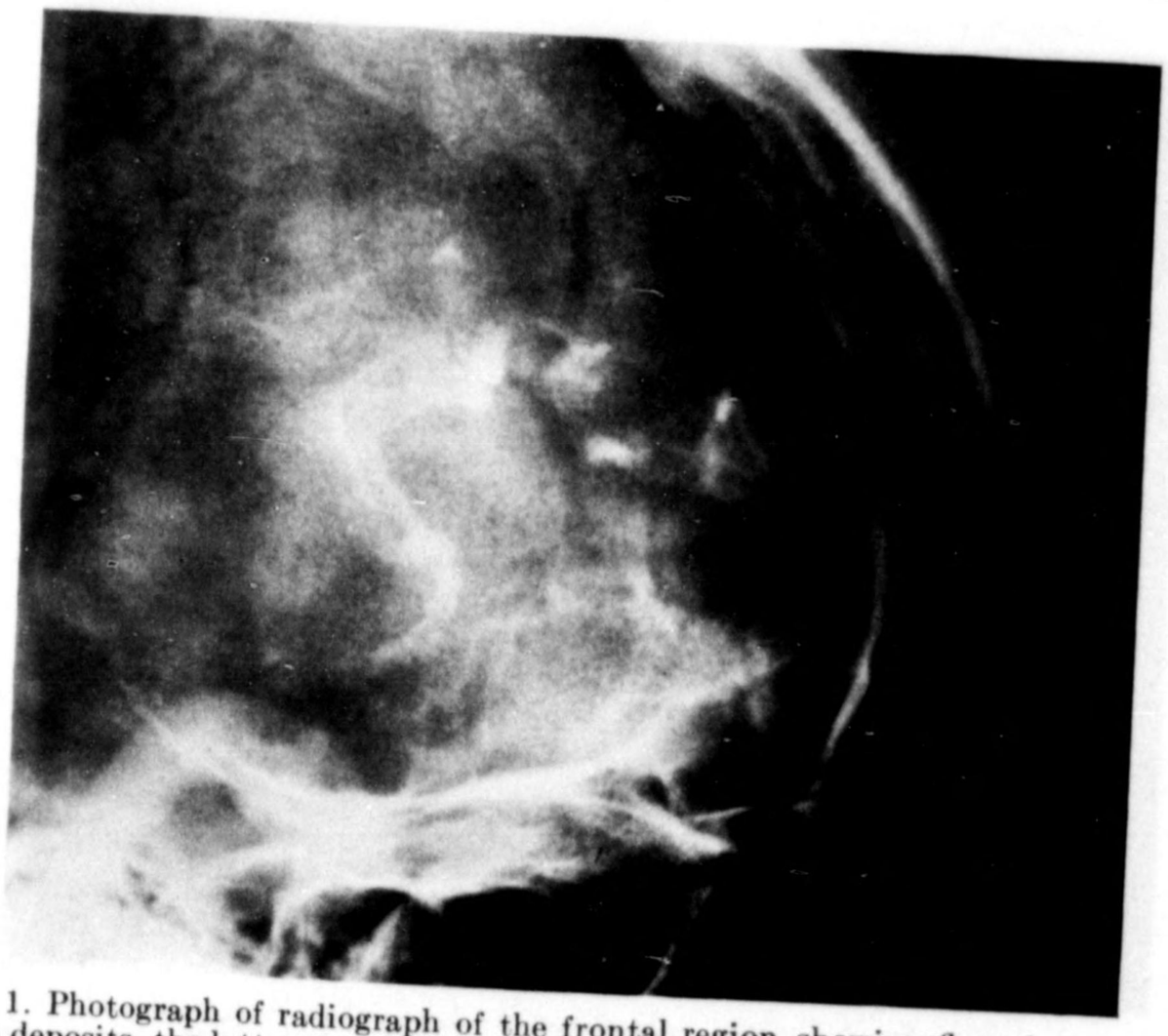

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euphoric, his speech was rapid, and current events did not seem to be well evaluated. No abnormal sensory, motor, or reflex changes could be detected.

Radiographs of the skull showed irregular calcification low in the region of the left frontal lobe (fig. 1). Some of the shadows in this region suggested partially calcified vascular channels. Other masses were small and irregular and quite widely distributed. There was an associated irregular hyperostosis of the adjacent inner table of the frontal bone. The floor of the anterior fossa on the left seemed eroded, and the composite shadow of the left lesser wing of the sphenoid and the orbital plate of the frontal bone had a frayed appearance suggesting erosion. The sella was oval and within normal limits, but there was a suggestion of erosion of the dorsum sellae and posterior clinoids.

Radiographs of the left shoulder showed a slightly comminuted impacted fracture of the surgical neck of the humerus extending into the greater tuberosity. The fragments were in good position and alignment.

Lumbar puncture disclosed an initial pressure of 360 mm. of water. The fluid was clear and colorless, and examination of the fluid gave normal results.

On February 15 an open reduction of the shoulder was done, and on March 18 a craniotomy was performed. A left frontal bone flap was turned down in the usual manner by one of us (P. J. V.), and, on opening the dura, the brain, except for a small strip along the posterior margin of the flap, appeared granular, was a dark red in color, and on palpation felt irregularly nodular. The frontal lobe was amputated back to the motor strip. This, however, did not remove the tumor in its entirety, as deep in the centrum beneath the motor area, tumor tissue with large calcified masses could be palpated. The day following the surgery the patient was fully awake, rational, and with no evidence of weakness of the right extremities. However, he was just as euphoric as he was prior to the operation. His recovery was uneventful, and he was discharged from the hospital on the 10th postoperative day.

Radiographs of the skull taken after surgery still showed the long linear masses of calcium present within the brain. The small irregular masses which lay in the fore part of the frontal lobe were evidently removed with the lobe at the time of operation.

The patient has been seen from time to time in the outpatient clinic and has presented no further symptoms, although recurrence of his trouble is to be expected, since a considerable portion of the tumor still remains *in situ*.

Evidently only a portion of the tissue removed at operation was forwarded to the Laboratory, for the total mass of the blocks of tissue (#46-1365) sent down was scarcely larger than a walnut. Frozen sections taken from the larger blocks were studied in connection with two of the larger masses which had been embedded in paraffin and from which sections had been taken and stained with hematoxylin and eosin. It was evident that two separate situations were to be described, one which was evidently a reaction of the cortex overlying the tumor, and the second, the nature of the glioma itself.

A study of a number of frozen sections taken from the overlying cortex disclosed the fact that there had been a profound alteration in the tissues of the cortex, which came to resemble an astrocytoma. Indeed, a study of the first sections led to this diagnosis. The lesion appeared to be a sparsely cellular growth which had replaced almost the normal architecture and cytology of the cortex, only the contour of the convolutions and the remaining leptomeninges betraying the fact that it was originally the cortical gray matter which had been so altered. The nuclei of the tumor cells were uniform in size, round or oval in shape, and filled with finely divided chromatin material which betrayed their neuroglial character. The various sections showed very little variability in the degree of cellularity of the neoplastic change from the various blocks of tissue. No degree of malignancy was thereby shown.

Here and there in the cortex could be seen small but variously-sized irregular calcospherites which represented evidently deposits of calcium in the small cortical blood vessels (fig. 2a). This change was not uniform throughout the altered cortex, for in many of the sections it was widespread (2b) while in others it was absent altogether.

The sections taken from blocks of the tumor proper disclosed an altogether different picture. Here four types of architecture could be made out, (1) focal areas which had a distinct fibrous appearance reminiscent of the peripheral neuromas, (2) areas in which large, typically ganglionic cells were present in abundance to the exclusion of almost all other elements (fig. 3a), (3) areas in which the great majority of cells were obviously of glial origin (fig. 3b), and (4) areas in which there was an intermingling of the large ganglionic and small glial elements. In addition, considerable portions of the sections showed more or less complete necrosis. The tumor tissue was broken up into irregular sections by connective tissue bands of varying width which formed a heavy stroma. Lymphocytes were found in varying numbers in various regions, being more abundant at the margins of the areas of degenerations.

The nature of the large cells was unmistakable. Their large size and irregular shape and multipolarity, the hyaline character of their cytoplasm, the vesicular character of their

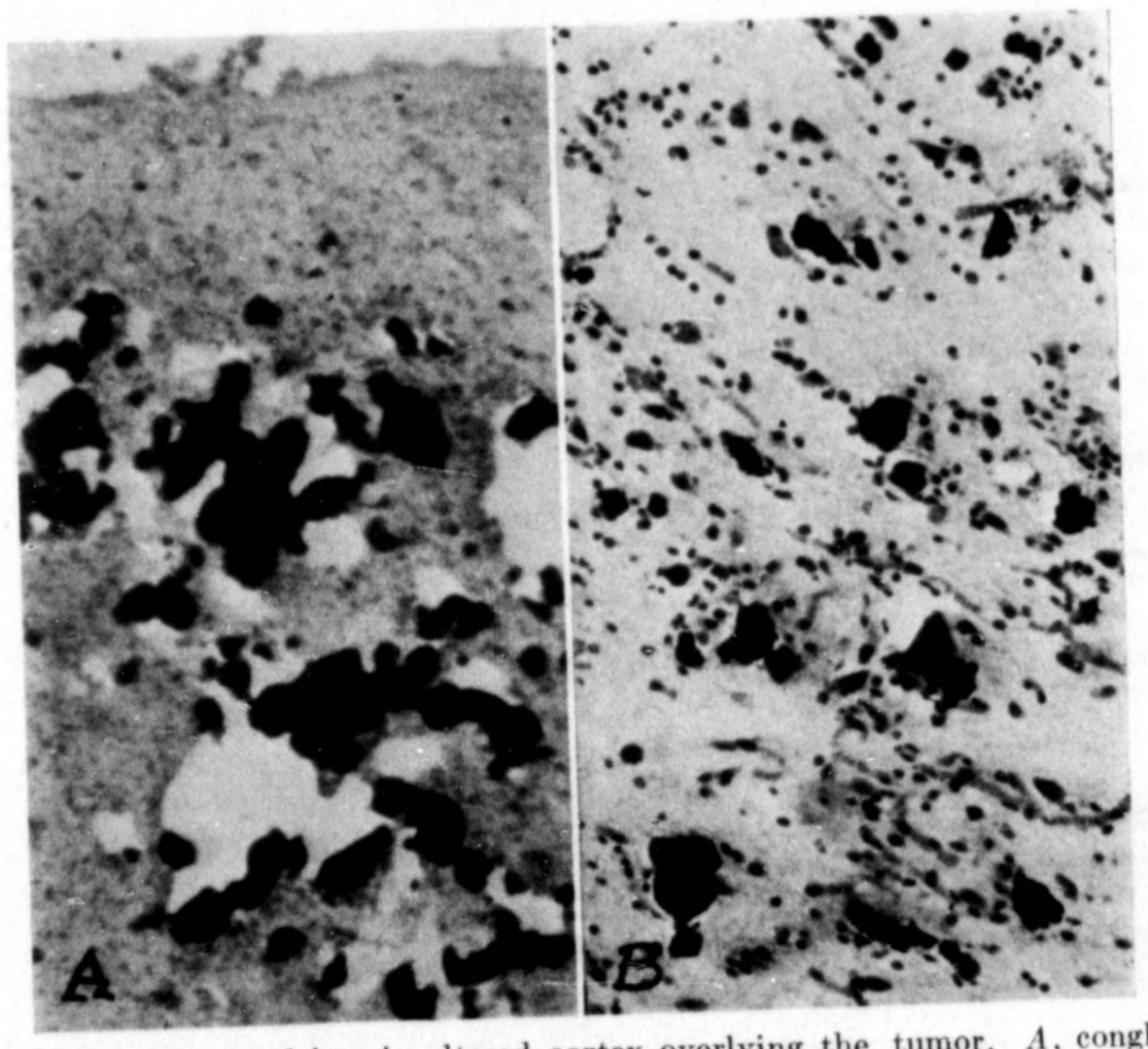

FIG. 2. Deposit of calcium in altered cortex overlying the tumor. *A*, conglomerate masses of calcium in an isolated portion of the cortex. H & E, × 37. *B*, scattered calcospherites in another region of the cortex. H & E, × 142.

one or more nuclei which contained a typical nucleolus, all indicated that these were ganglionic elements (fig. 4). As is the rule, no tigroid substance could be seen in these cells. The greater majority of these elements were evidently quite mature, although smaller unipolar and bipolar cells were also to be found. In areas of the tumor where these cells were almost exclusively present, a striking appearance was presented.

The smaller elements were obviously glial in character, as their typical nuclei indicated. In some portions of the tumor these cells constituted the majority of the cellular elements, but they were found almost everywhere in the sections studied. The cytoplasm of these cells was quite scanty and the outline of the individual cells was scarcely ever seen.

For the most part, the tumor was well vascularized, with small, medium-sized and large blood vessels being found in abundance in most portions of the tumor. There was some

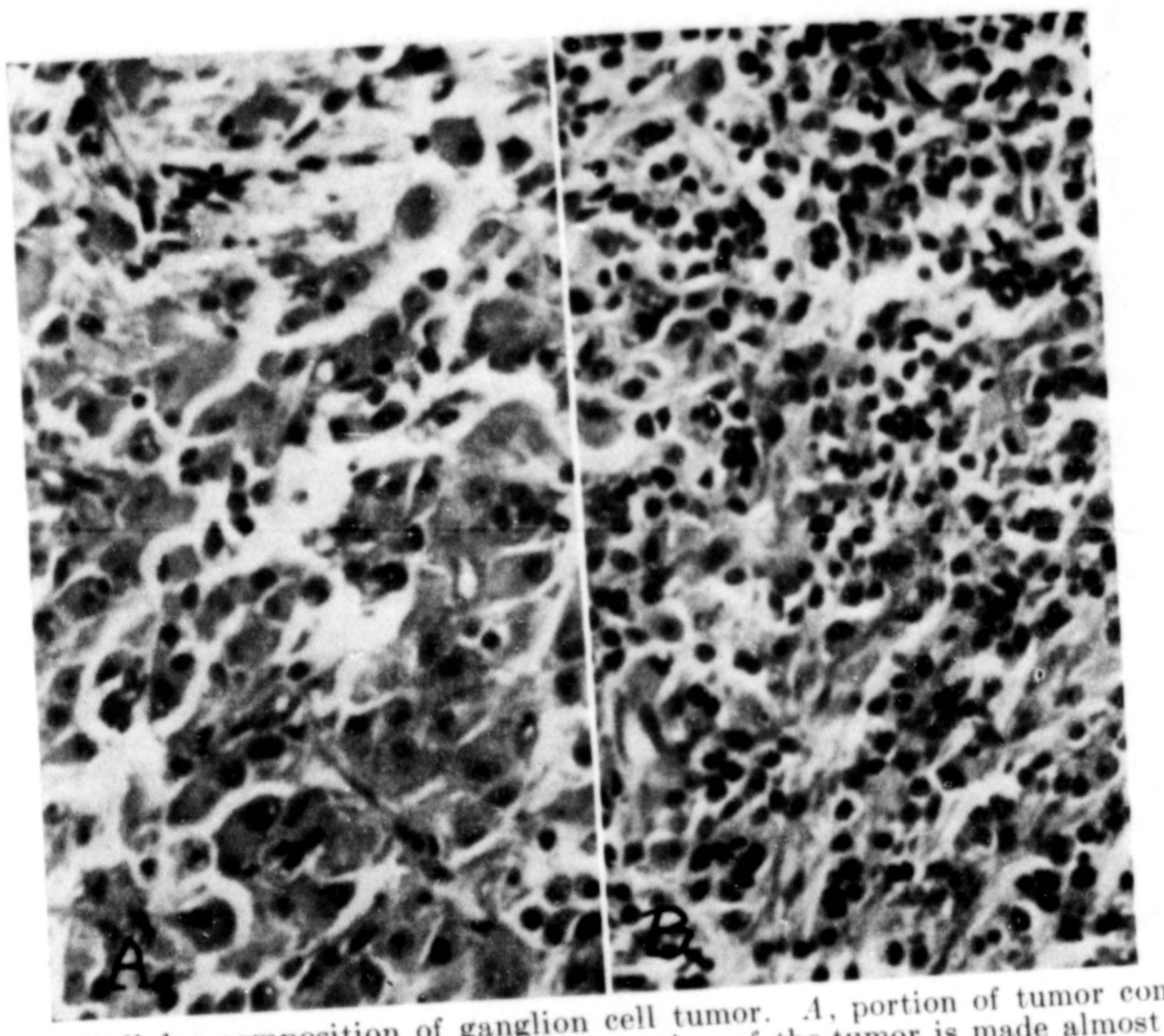

FIG. 3. Cellular composition of ganglion cell tumor. *A*, portion of tumor composed largely of neoplastic ganglion cells. *B*, this portion of the tumor is made almost exclusively of gliogenic cells. Both sections H & E, × 300.

FIG. 4. Neoplastic ganglion cells showing multipolarity, hyaline character of cytoplasm, and typical vesicular appearance of their nuclei. H & E, × 705.

evidence of pathologic alterations in some of the vessels in the form of endothelial proliferation and thrombosis which evidently accounted for the large areas of necrosis. The smaller areas of necrosis were somewhat reminiscent of those found in the glioblastomas, except that no bordering pseudopalisades were present, only scattered lymphocytes.

Some of the blocks of tissue removed at the time of operation were evidently not forwarded to the Laboratory for only occasionally was calcification discovered in the sections from the tumor proper. In particular were there found no deposits of calcium in the walls of the larger blood vessels as was suggested by the radiographs of the skull. Nevertheless, there was found sufficient evidence to the effect that many of the smaller blood vessels were the seat of calcium deposits. Some of these vessels were transformed by this process into calcareous tubes (fig. 5). Some of the calcospherites may have been formed within the connective tissue masses which formed the stroma. It is to be presumed that a similar and much more conspicuous alteration would have been found in the larger vessels.

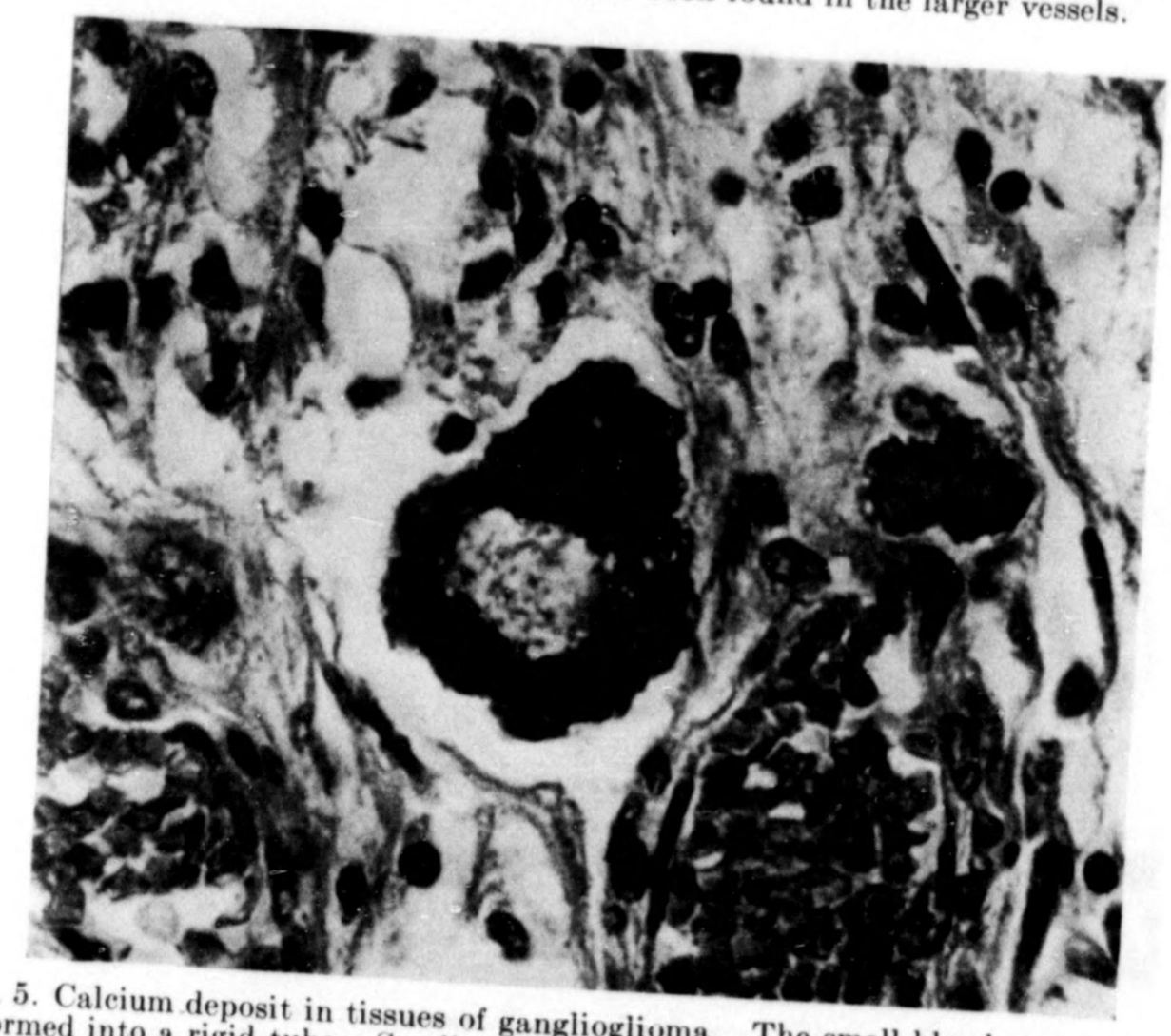

FIG. 5. Calcium deposit in tissues of ganglioglioma. The small blood vessel has been transformed into a rigid tube. Smaller mass at the right may have been deposited in a smaller blood vessel. H & E, × 705.

Comment. In this case, we have to deal with a classic ganglion cell tumor of the left frontal lobe of the brain, evidently one of long standing in spite of the paucity of clinical symptoms, which constituted essentially a frontal lobe syndrome. Among the several points of interest are the almost pure neurogenic character of some portions of the tumor, the presence of extensive areas of necrosis, the neoplastic reaction of the overlying cortex, and, to the present point, the deposit of calcium salts both within the tumor itself and in the overlying altered cortex. As has already been pointed out, the occurrence of calcium, both within ganglion cell tumors and in the adjacent cerebral tissues, is not necessarily uncommon and constitutes one of the reactions of adjacent nervous tissue to tumors of the glioma group of almost every variety.

CALCAREOUS DEPOSITS IN GLIOMAS

As has been pointed out by one of us(C. B. C.),[1] the occurrence of calcium as a process in connection with gliomatous tumors of the brain may present a variety of different patterns. Small calcospherites may be found scattered more or less evenly throughout a tumor (characteristic of astrocytomas). In other cases (also commonly in astrocytomas), small globules or spherules may be found in the walls of blood vessels within the glioma. These may be isolated or conglomerate; in the latter case they may transform the vessel into a rigid calcified tube or occlude it altogether. In a third group of cases, the collection of calcareous salts may form a considerable more or less solid mass, usually at the center of the tumor. While this may be the result of fusion of a number of calcified blood vessels in some instances, in others it is evidently the consequence of deposit of these salts in an area which has previously undergone advanced regressive changes.

It was also shown in the study just cited that while calcium is commonly if not predominantly deposited in the walls of blood vessels, it may be found in isolated globules in the tumor cells, in the stroma, or even in such adventitious structures as blood cells or in corpora amylacea. In the tumor cells, the process occurred either in the cytoplasm or the nucleus.

One must also consider the occurrence of calcareous particles in the nervous tissues at the margins of tissues. This alteration may be found at the margins of fairly rapidly growing tumors such as glioblastomas as well as the ones of slower evolution, notably the astrocytomas and the gangliogliomas. This has been interpreted in case of the latter as being due to an interference in tissue respiration by pressure on the adjacent tissues by the expanding tumor. Whatever be the situation, the cause is very likely the same for all types of tumors.

It is perhaps one of the prime purposes of this study to point out the fact that even the larger vessels which become engulfed by the growth of a glioma may become so heavily infiltrated with calcium salts as to outline the structure of the vessel in roentgenograms of the skull. This is evidently not a common type of change, for it has not been described elsewhere insofar as the present writers are aware. While it is to be regretted that the surgical specimen did not include a portion of one of the larger calcified vessels in order to demonstrate the possibility beyond argument, its occurrence in an astrocytoma in the same location as observed by one of us (C. B. C.)* would seem to make clear that this is the nature of the process so distinctly portrayed in radiographs of the skull in the case here under consideration.

CALCIFICATION IN GANGLIOGLIOMAS OF THE BRAIN

A study of the reported cases in which calcium deposits were found in ganglion cell tumors of the brain as well as in the cases which have come to the attention of

* In the case mentioned (to be reported later), a woman in her early twenties presented herself at the Clinic with generalized convulsions and signs of frontal lobe involvement. The occurrence of a typical vascular pattern in the roentgenograms led to the diagnosis of a left frontal angiomatous malformation and to the administration of radiation therapy. At autopsy, an astrocytoma of the lower and mesial aspects of the frontal lobe was disclosed.

the present writers makes it evident that these changes are of a definite pattern which is applicable to the entire group of gliomas. In other words, the deposit of calcium represents a *process* of change, one which is not particularly characteristic of any one variety of glioma. To be sure, there are some variations, such as the central deposit in some types of gliomas, but even here one is scarcely justified in presuming beyond certain limits the histologic type of tumor on the basis of the appearance of the shadows in radiographs of the skull.

In the case of ganglion cell tumors, it becomes evident that the deposits within the tumor may be scattered (case of Courville and Anderson[11]), or found within the walls of the blood vessels (case of Bielschowsky[6]). In the case here at hand it also becomes apparent that even the larger vessels (perhaps the anterior cerebral arteries) which have been enveloped by the growing tumor may be so surcharged with calcium salts as to make it possible to trace their somewhat displaced course in radiographs of the skull. This seems to be an uncommon type of alteration, and the location in the frontal lobe may have something to do with it, since it occurs in other gliomas in this same location (see previous footnote).

For some reason, it is evident that the deposit of calcium in the nervous tissues, either cortical or subcortical, at the margins of ganglion cell tumors is fairly common. This is very likely to be accounted for by their unusually slow growth which results in progressive compression of these tissues with consequent interference with tissue respiration. This seems to be characteristic of such tumors of the temporal lobe (case of Bielschowsky and Henneberg[8]) in contrast with the group originating in the floor of the third ventricle (cases of Robertson,[3] Josephy,[4] Macpherson,[5] Perkins,[7] Foerster, McLean and Gagel[9]), in which the calcium deposits are found within the tumor itself. It is also true of certain of the cerebellar gangliogliomas of the diffuse type. Here one often finds unusually heavy and often condensed calcospherites both within the regional cortex and in the subcortical white matter (cases of Bielschowsky[6] and Bielschowsky and Simon[10]). It is possible to say, therefore, that with the certain exception of the group of cerebellar gangliogliomas with unusual patterns of calcification in the regional tissues (cerebellar gliomas of other types are rarely accompanied by deposit of calcium), one may demonstrate in gliomas of other types the same patterns of deposits as in this particular subgroup.

SUMMARY

1. Since the deposit of calcium is not uncommon in tumors of the glioma group, particularly those of slower evolution, it is not surprising that calcospherites occur in ganglion cell tumors of the brain, which are among the most benign of all primary tumors arising from nervous tissue.

2. A study of the cases reported in the literature would suggest that in a fair percentage of the cases calcium is found either within the tumor or deposited in the nervous tissues at its margin. Tumors arising from the floor of the third ventricle seem to be more commonly the seat of calcium deposits than the other anatomic groups. The exact incidence of calcification cannot be accurately de-

termined, since it is obvious that some reporters have ignored the change as incidental and not worthy of mention.

3. A case with heavy condensation of calcium in the larger vessels of the left frontal region presumably engulfed by the tumor, as demonstrated radiographically, is reported herewith. A considerable mass of the tumor was successfully resected at operation.

4. According to this case and the others reported, it would seem that the calcium may be deposited within ganglion cell tumors in the form of isolated calcospherites or in the walls of the blood vessels, either large or small. In the former instance, which is evidently quite rare, the characteristic formation may be clearly distinguished in radiographs of the skull. The question is raised whether this is a characteristic alone of the frontal regions, where rarely other slowly growing gliomas may provoke the same reaction, or whether it may occur elsewhere as well.

5. As is also true of other slowly growing gliomas, calcium may be deposited in the walls of blood vessels in the nervous tissues at the margin of the tumor, whether cortical or subcortical. This has been explained on the basis of an interference in tissue respiration by the gradual compression of these tissues by the slowly expanding tumor.

6. It is particularly pertinent to point out that this extraneoplastic deposition of calcium occurs in the cerebellar as well as in the supratentorial group of ganglion cell tumors, where it may form a peculiar heavy localized meshwork somewhat unusual in its appearance. This is significant, perhaps, since in infratentorial gliomas of other types calcium salts are rarely found.

7. Since the deposit of calcium in ganglion cell tumors follows in general the pattern as seen in other gliomas, one cannot make a diagnosis of this variety of tumor on the basis of roentgenograms of the skull. One can only include it with the astrocytomas and the oligodendrogliomas as a possibility when such deposits are discovered radiographically.

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THE ANGIOBLASTIC GROUP OF MENINGIOMAS*

A STUDY OF THIRTEEN VERIFIED CASES

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To many Pathology is essentially a dead science, one to be pursued for intellectual ends alone. Ignoring the important principle which gave this science its birth,—i.e., that the physician should seek for an explanation of manifestations of disease in the bodies of the dead,—the recent tendency has been to make the study of diseased tissues an abstract effort whose findings contribute only indirectly and often remotely to the humanitarian objectives of Medicine. But clinicians today have to learn the basic concepts of disease in the same way as did physicians of three centuries ago—at the autopsy table. The necessities which influenced Bonet to write the *Sepulchretum* still exist today, although to be sure, in a more widely extended and ramified form.

Neurology has suffered much from its separation, for whatever reason, from Pathology. Too often the clinical neurologist is unable to attend the necropsy and, instead of its being preserved for a more thoughtful study, the brain is assiduously reduced to hopeless confusion after the time-honored but antiquated method ascribed to Virchow. Beyond all hope of reproduction by photography or of critical study in light of the clinical picture, the remains, perhaps enshrouding a priceless lesion, are consigned to oblivion in the victim's coelomic cavity and the case is forever closed.

Standing out in strong contrast to this deplorable situation was the practice at Doctor Cushing's clinic at the Peter Bent Brigham Hospital in Boston. In the relatively few cases which met their end at the Hospital, the brain was carefully removed after preliminary fixation with formaldehyde passed through the carotids and further preserved in formaldehyde to complete the process. Whenever the press of circumstances permitted, it was Doctor Cushing himself who sectioned the specimen and indicated the photographs to be taken. A picture never to be forgotten by those of us fortunate enough to be attached to the Clinic in one capacity or another was that of the "Chief" in his gray operating gown sitting at the long

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bench before the north window in the Laboratory quietly and unhurriedly scrutinizing the brain with the patient's record open before him.

One of the really great contributions of Cushing to the surgery of intracranial tumors was the introduction of the principle of evaluating the neobiologic activity of a given lesion by the length of time its victim survived, of interpreting the microscopic picture in the light of clinical manifestations. To him, Pathology was not a dead but a living science, not one to be pursued in the recesses of the laboratory but one which was to serve as a *Diener* to the clinician at the bedside and to the surgeon at the operating table. Only in this way, in his opinion, could the laboratory achieve most definitely and completely its humanitarian objectives. On several occasions, the senior author of this study has heard Doctor Cushing say that the final answer in any given case was not to be found alone by the microscope but in a survey of the entire problem,—an investigation into the course of the disease, the nature of the lesion as exposed at operation, the postoperative course and the length of life which is vouchsafed to the patient. The microscope, symbolic of the laboratory, was but one of the avenues through which the ultimate truth was to be reached.

The story of the angioblastic meningiomas is but an example of this important truth. A tumor, grossly typical of a "dural endothelioma," which had been variously diagnosed microscopically in the Boston Clinic after repeated operative resections as a "glioma," an "endothelioma"—possibly an "endothelial sarcoma," was finally designated fifteen years later as a "meningioma of angioblastic elements with tendency to sarcomatous transformation"[1]. In the decade which passed between the publication of the study which was to christen one variety of tumors of the meningioma group and the recent monograph on meningiomas by Cushing and Eisenhardt[2], it came to be recognized that, instead of a single type of tumor, the angioblastic meningiomas constituted a constellation all its own.

It is the purpose of this study to review the literature on this interesting lesion, to report the findings in a series of thirteen lesions of this type which have come to our attention in the Cajal Laboratory and to discuss the possible significance of the obvious variations in their structure.

HISTORICAL SURVEY

In the case of the angioblastic group of meningiomas, tumors whose identification depended upon a wide general knowledge of meningiomas in particular and of blood-vessel tumors in general as well as upon certain refinements in histologic technique, it is natural to find that development of the concept of a variety of meningeal tumors containing angioblastic elements is relatively recent. On the other hand, it is too much to believe that the entire idea has emerged, full blown from the crysallis of that group

of tumors known since the year of Cushing's birth as *endotheliomas*, having been so designated by Camillo Golgi in 1869.

Until the essential nature of the meningiomas was understood, it could scarcely be hoped that the character of one of the variants could be fully appreciated. Nevertheless, since angioblastic tumors are not uncommon, it is to be expected that some expressions as to the vascular character of this tumor are to be found in the voluminous literature on meningeal tumors. Such is quite the case. Even during those early decades when tumor nomenclature was based largely on architectural arrangement or structural appearances, the large number of small blood vessels constituting the major portion of these tumors made its impression. Since meningiomas were early designated as sarcomas (in spite of Golgi's recommendation), a type of tumor found to contain an unusual number of blood vessels was commonly designated as *angiosarcoma* or *plexiform angiosarcoma*. The ubiquitous Bramwell[3], early to follow the lead of contemporary pathologists, describes quite at length such a vascular tumor and several drawings of it are included in his monograph, one of which is shown herewith (fig. 1). This designation was soon utilized by other neurologists, such as Knapp[4], who briefly mentioned this type of tumor in his Fiske Fund essay. As early as 1896, Auvray[5], interested in the surgical aspects of intracranial tumors, mentions the "forme telangiectasique" of sarcomas which bled profusely in the course of an operation. In view of the current designation of meningiomas as "sarcomas," (i.e., *sarcome angiolithique*), it is possible that Auvray may have had such a tumor in mind.

In his classic monograph on tumors in general, Borst[6] described certain tumors arising from the pia mater which had a plexiform structure and which he called a *perithelioma* after the suggestion of pathologists such as Axel Key. This name seems to have been applied to tumors whose numerous vessels seem predisposed to undergo hyaline change. This is now recognized to be one of the predominant characteristics of the tumors here considered. Borst did not clearly distinguish these peritheliomas from other tumors arising from the dura mater which also had a highly vascular structure which he named *hemangioendotheliomas*. Still other tumors were described under the title of *lymphangioendotheliomas* and *cylindromas*. As long ago as 1902, therefore, it became evident that several varieties of highly vascular tumors arose from the membranes of the brain. Could we at this date properly evaluate the details of these descriptions, no doubt some of the subtypes of the angioblastomas might be distinguished. Ribbert[7] also adopted this nomenclature, but distinguished "angiosarcomas" and "peritheliomas" from the larger group of meningeal tumors.

As time went on, the group of dural tumors came to be separated from the more malignant sarcomas, and their designation as "endotheliomas"

was more widely accepted. The more vascular varieties were consequently named *plexiform endotheliomas* or *hemangioendotheliomas*. Bruns[8], after the lead of Birch-Hirschfeld, emphasized the fact that these blood vessels were newformed and therefore an integral part of the tumor. In this important conclusion, we have one more important fact in the history of this interesting neoplasm, that its constituent cells possessed a multipotentiality. This observation was made many times before by investigators who distinguished certain fibrous elements in some of these dural

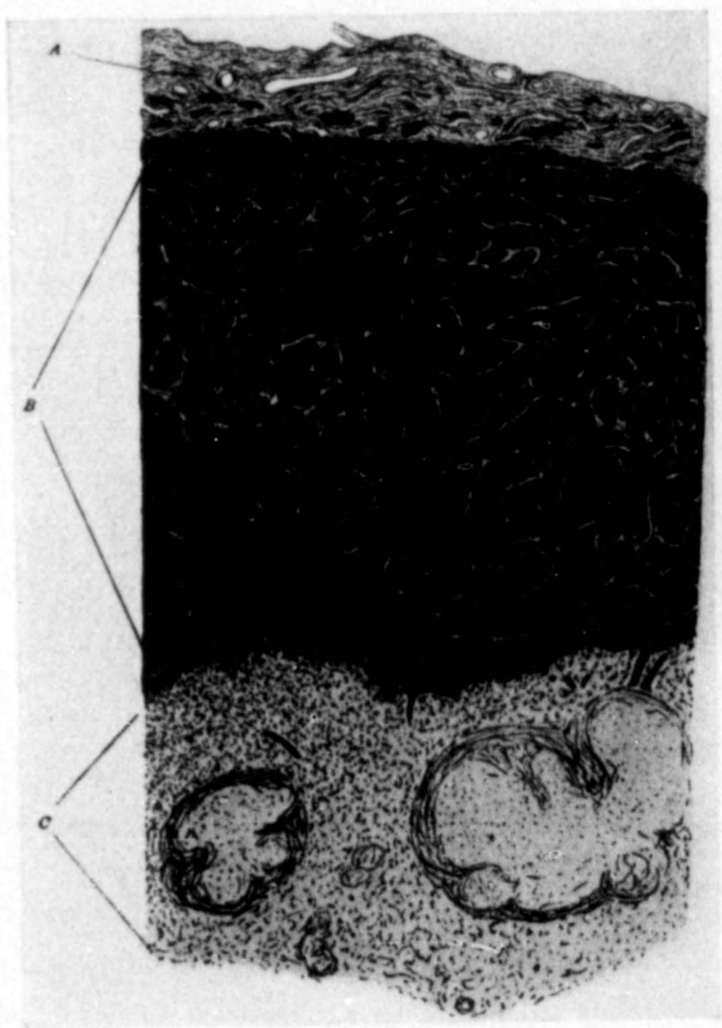

FIG. 1. Bramwell's camera lucida drawing of microscopic section of a "plexiform angiosarcoma." This vascular tumor, adherent to the under surface of the dura mater which is also invaded by it, is probably an angioblastic meningioma.

tumors (*Plattenzellensarkom, Sarcoma planocellulare, Sarcoma endothelioides fasciculatum or Endothelioma fasciculare*) in contrast to other similar tumors of the dura made up of rounded cellular elements grouped in masses or clusters (*Endothelsarcom, Sarcoma endotheliale, Alveolärsarcom, Endothelioma alveolare, diffusum or proliferans*)[6].

Here the matter seemed to rest until Bailey, Cushing and Eisenhardt[1] again called attention to a group of three such tumors in 1928 and described them as *angioblastic meningiomas*. In the intervening twenty years since the monograph of Bruns was published, interest in the matter of classifi-

cation of tumors of the brain had lagged, observers being content to designate the relatively rare examples of vascular tumors of the meninges as peritheliomas or cylindromas after the lead of their forebears.* No doubt a critical survey of individual reports of meningeal tumors would disclose many additional cases of this interesting lesion. For example, Blackburn[9] described quite in detail a series of seventeen cases of dural tumors in twenty-eight neoplasms of the intracranial space found in autopsies performed at the Government Hospital for the Insane. Two of these seventeen cases (Cases 1178 and 539) are almost certainly angioblastic meningiomas. In the first case, the carefully written description is almost unmistakable: "Large bands of connective tissue . . . apparently hyaline . . . contained many large blood vessels, often with thick hyaline

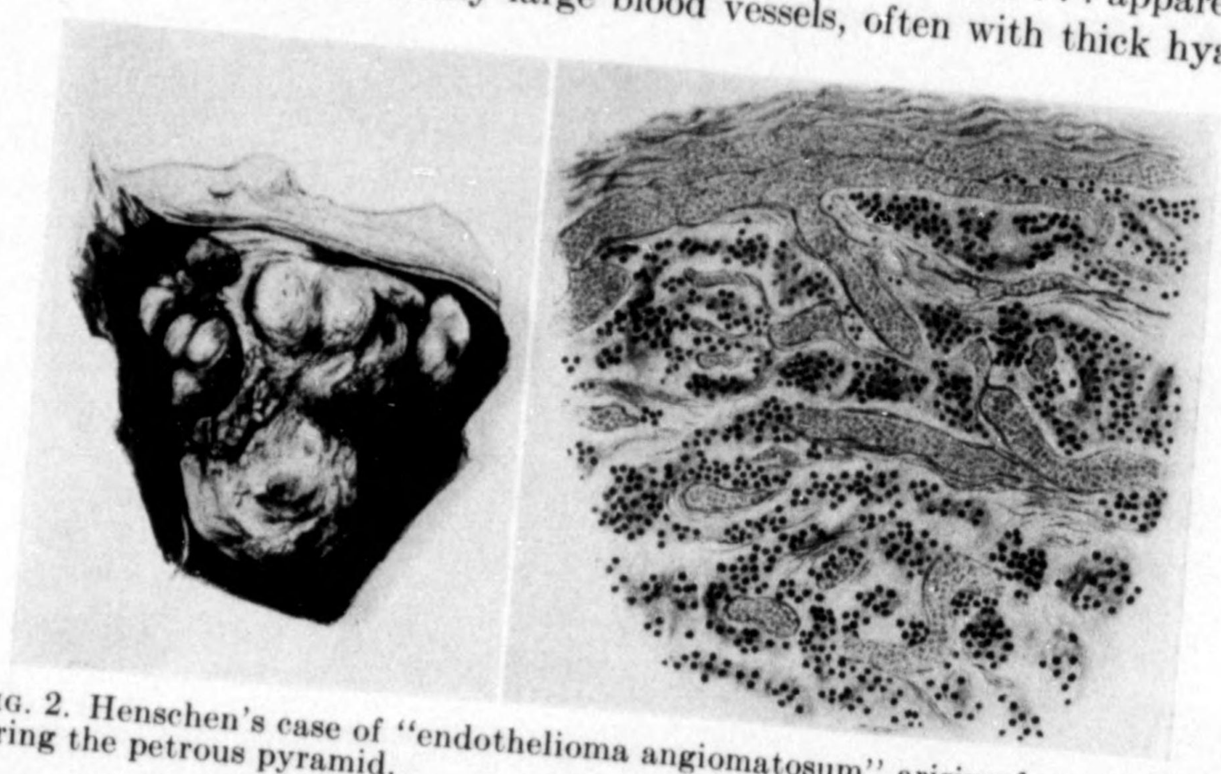

FIG. 2. Henschen's case of "endothelioma angiomatosum" arising from the dura covering the petrous pyramid.

walls, and many blood channels without definite walls other than a layer of endothelium separating the channel from the surrounding tissue. In some places these channels were very numerous, giving almost the appearance of angioma." Again Henschen[10] illustrates and describes what seems to be a typical case of an angioblastic meningioma of the posterior fossa (Case 15) designated as an *endothelioma angiomatosum* (fig. 2).

After the appearance of the original article on the subject by Bailey, Cushing and Eisenhardt, in which three cases were reported, Bailey[11] reported still another case of this tumor removed surgically from the temporal lobe. In 1930, del Río-Hortega[12] described three varieties of vascular meningiomas as "angiosarcomas," "exotelioma vascular" and

* Mallory's designation of vascular meningiomas as "hemangioendotheliomas" is simply an adoption of the term utilized by Bruns several years earlier.

"exotelioma angiomatosa" which are closely related to if not identical with the three varieties of Cushing and Eisenhardt. Six years later, Bergstrand and Olivecrona[13] reported four additional cases. In 1936 Wolf and Cowen[14] reported six cases from the New York Neurological Institute. Globus[15] evidently studied several examples in his article on the classification of meningiomas but does not state how many of the various subtypes were included in 103 meningiomas which constituted his material. In their monograph on the meningiomas, Cushing and Eisenhardt[2] reported 23 cases which included the four previously reported by Bailey, Cushing and Eisenhardt[1] and by Bailey[11]. To this growing list, the writers wish to briefly record the essential facts of the thirteen cases which constitute their own series of definite examples of angioblastic meningiomas.

REPORT OF CASES*

The cases in our series will be divided into four groups but only three of these groups will correspond with those of Cushing and Eisenhardt. We shall reverse these three types, progressing in what seems to us a more logical fashion from the purest form to the fourth type in which an admixture of typical mesotheliomatous tissue may be found.

Type I. Leptomeningeal (Hem-)angioblastoma

This tumor is, beyond all question, a pathologic entity as a study of the reported cases and of our own material clearly indicates. It corresponds closely to, if it is not identical in structure with, the hemangioblastomas of the cerebellum. It has been variously designated as an *exotelioma angiomatosa* (del Río-Hortega[12]), *meningioma piale* (Globus[15]) and *angioblastomatous meningioma* (Cushing and Eisenhardt[2]). These tumors are characterized by the presence of many capillary spaces of quite uniform size in a poorly cellular stroma, the nuclei of the tumor cells being embedded in a feltwork of reticulin. In some instances, the cells show some tendency to malignant change. Cushing and Eisenhardt[2] subdivide this group into *those predominantly cellular and those predominantly capillary*. Three of our cases were of this type, the tumors in two cases being located in the left parasagittal region and one in the region of the pterion.

Case 1. *Case of Drs. V. L. Andrews and O. I. Cutler.* (H. H. No. 31-050). A white woman, aged 60, was admitted to the hospital on Dec. 19, 1929, in *status epilepticus*. On recovery she complained of pain in the left frontoparietal area. In 1897, the patient had fallen from a bicycle following which she had had a generalized

* For sake of brevity, only those details of the cases which might prove of value to anyone making a complete survey of this variety of tumor have been given. While the pathologic studies of all the examples of tumors herein reported were made in the Cajal Laboratory by the senior author, we have chosen to designate the individual cases wherever possible by the names of the neurologists and/or neurosurgeons who had the patients under their care. In some instances the patients had no adequate clinical study, the specimen being brought to the Laboratory by an interested friend.

convulsion. Convulsive seizures had occurred thereafter at intervals of from six months to a year. After 1915, the seizures were followed by transitory weakness and numbness in the right foot, and after 1926 the right arm became weak and painful. The seizures had become increasingly frequent before her death, which occurred thirty-two years after the accident, and three years after definite onset of motor weakness. No report of radiographs of the skull were available. At autopsy

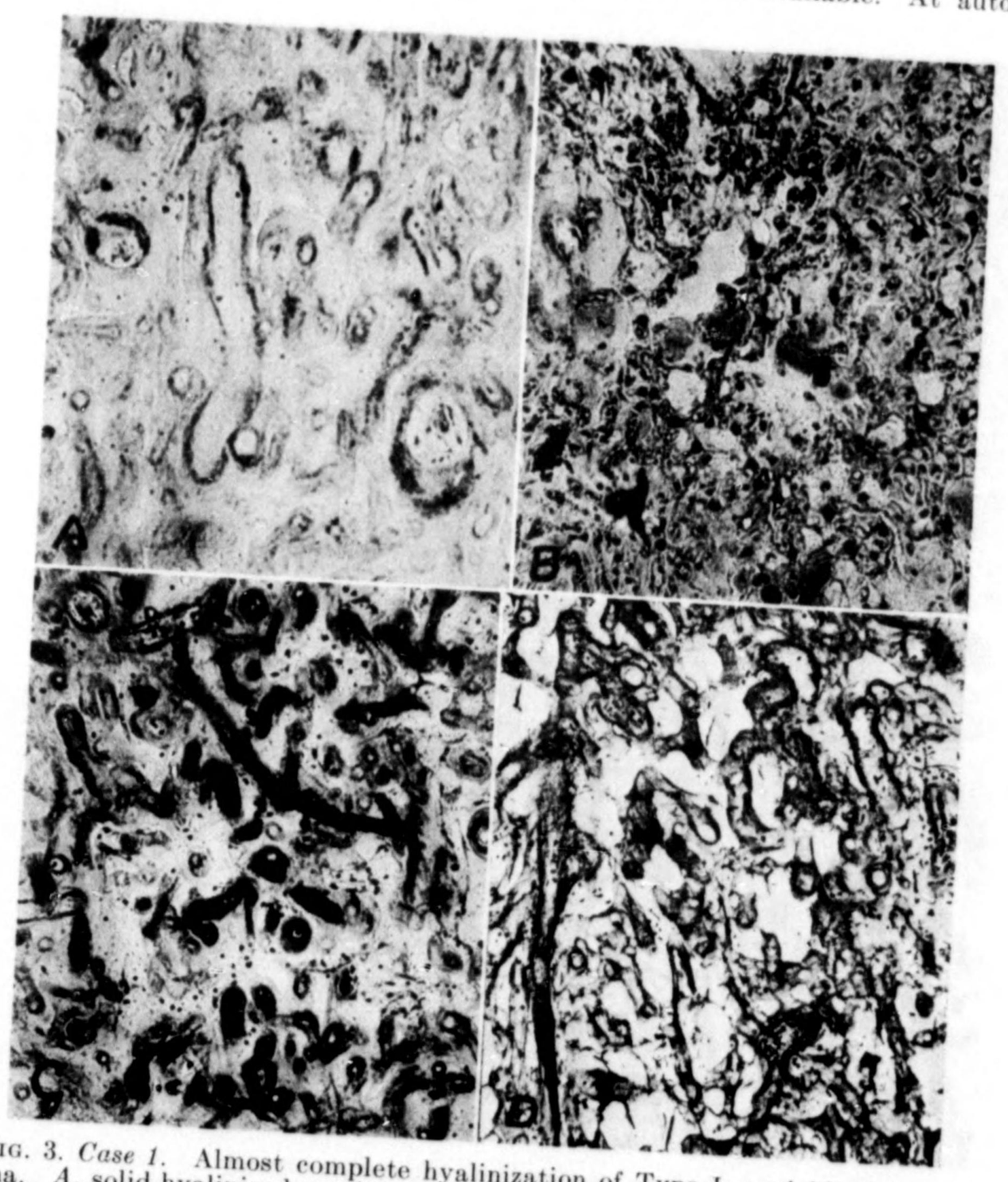

FIG. 3. *Case 1.* Almost complete hyalinization of Type I. angioblastic meningioma. *A*, solid hyalinized portion of the tumor; *B*, better preserved foci suggesting leptomeningeal angioblastoma; *C*, calcareous "dust" in walls of blood vessels. All H. & E., × 73; *D*, Perdrau method showing network of reticulin.

(M-17), a firm tumor, 3.4 x 3 x 3 cm. in size, was found attached to the left side of the falx cerebri in the central area. It was separated from the brain by a large cystic cavity which lay parallel to its outer surface. The tumor was found to be almost completely hyalinized but fairly typical areas in scattered parts of the section showed structure characteristic of a *meningeal angioblastoma*. Many of the hyalinized vessels showed calcareous "dust" in their walls. The characteristics of the tumor are shown in the accompanying plate (fig. 3).

Case 2. (L. A. C. H. No. 316–368). A white woman, aged 56, was admitted to the Hospital on Oct. 25, 1934, with signs of acute bronchopneumonia from which she died two days later. Two years before, she had suddenly collapsed after which an advanced left hemiparesis was observed. A diagnosis of diabetes mellitus, Bright's disease and a "stroke" had been made at the time. An examination just before death revealed a spastic left hemiplegia with exaggerated deep reflexes on this side. No radiographs of the skull were taken. She had survived apparently for an interval of two years. At autopsy (# 12–463), performed by Dr. E. F. Mauer, an irregular, reddish colored tumor, measuring 7.5 x 5 cm. in its transverse diameters was found arising from the dura in the region of the right pterion and compressing the adjacent frontal and temporal lobes. Microscopic examination showed the tumor to be a typical *meningeal angioblastoma* with considerable hyalinization

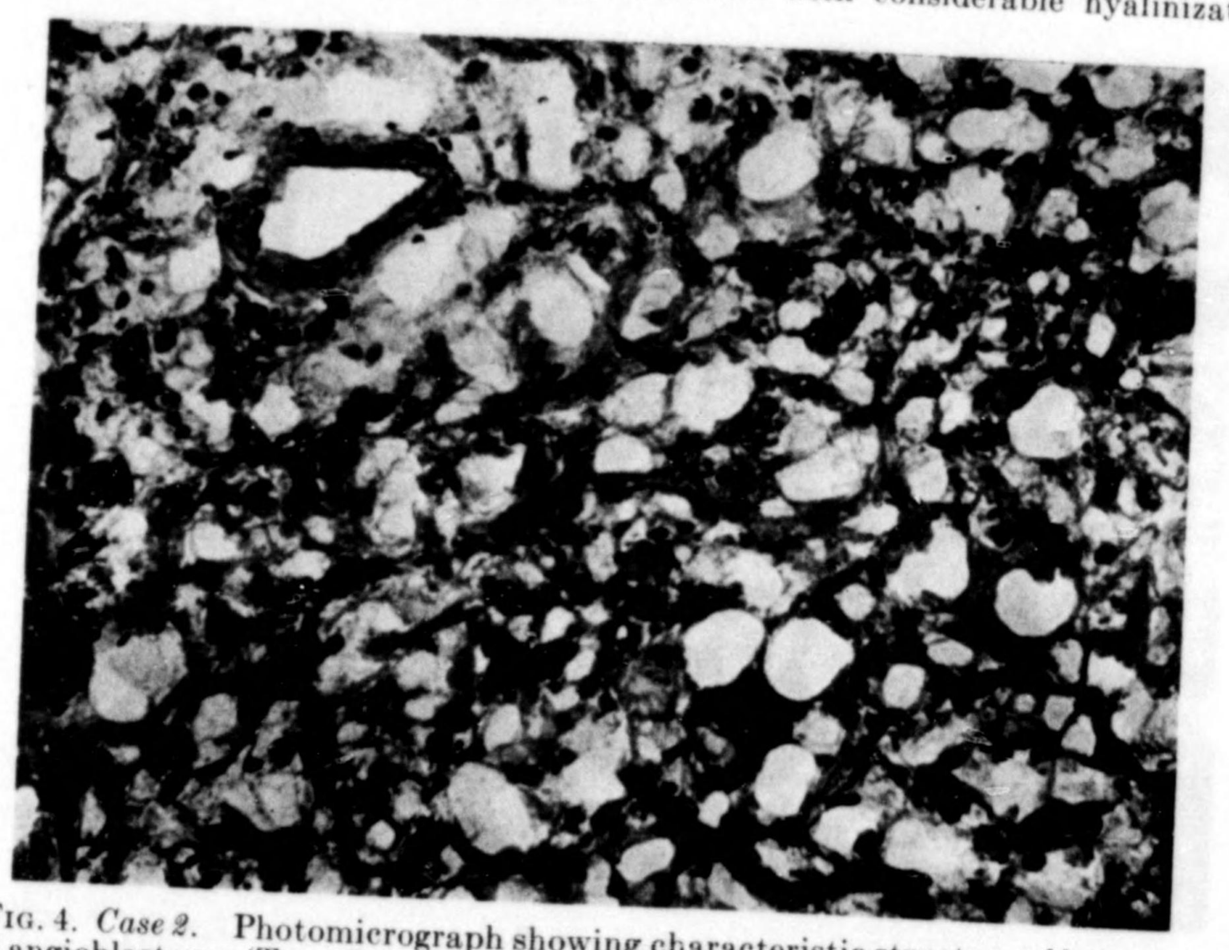

FIG. 4. *Case 2.* Photomicrograph showing characteristic structure of leptomeningeal angioblastoma (Type I). H. & E., × 110.

of the walls of its blood vessels. A few areas of cellular proliferation, indicative of increased neobiologic activity were noticed. Deposits of calcareous salts were observed in the form of "dust" in the walls of the larger blood vessels, as calcospherites in the walls of the smaller vessels, and occasionally as typical psammoma bodies.

Case 3. *Case of Dr. R. B. Raney.* (L. A. C. H. No. 472–727). A white painter, aged 57, was admitted to the Hospital on Oct. 8, 1936, with the complaint of right-sided jacksonian seizures for five years, frontal headaches for three years and weakness in the right leg for nine months. An effort had been made in another hospital to explore the left parietal region in May of 1936, but technical difficulties precluded completion of the operation. A series of x-ray treatments had been given thereafter. An examination at the time of entry had disclosed a slight elevation of the bone flap, a slight right hemiparesis and hemihypesthesia, and increased deep reflexes on the

right side without pathologic toe signs. A ventriculogram showed a depression of the lateral ventricles from above. Erosion of the anterior margin of the flap was also shown. Re-elevation of the bone flap on Oct. 26, 1936, by Dr. R. B. Raney disclosed a large left parasagittal tumor. The tumor (# F-8540) was completely removed at a second session (Nov. 5). It measured 4.1 x 3.2 x 2.4 cm. When last seen on Oct. 29, 1939, a slight right hemiparesis and hemihypesthesia was still evident but the seizures had not recurred. The tumor proved to be a typical *meningeal angioblastoma* (fig. 4), with many foam cells about some of the sinusoids, occasional calcospherites and much hyalinization of the blood vessel walls.

Type II. Transitional Angioblastic Meningioma

While this tumor also seems to be a clear-cut neoplastic entity, it is not so definitely a pure tumor in the same sense as Type I. In our examples, only certain portions of the section presented a typical appearance, others showed fairly solid cellular areas with relatively few sinusoids. If it is true, as suggested by Cushing and Eisenhardt[2], that these solid areas of tissue and the cell strands between the sinusoids are of meningothelial character, then Type II is simply a step in the direction of the typically meningotheliomatous meningiomas. In other words, we are dealing with a meningioma which has a distinct and strong tendency to angioblastic activity. Its relationship to Type I, on one hand, is suggested by the arrangement of its reticulin net; to the meningothelial tumors, on the other, by the extensive syncytial areas of cells which are evidently not of fibroblastic character. They, too, may show evidence of increased neobiologic activity. This type has been designated as an *exotelioma vascular* (del Río-Hortega), *meningioma piale* (Globus) and *transitional angioblastic meningioma* (Cushing and Eisenhardt).

Three tumors of this type have come to our attention, the first an incidental posterior fossa nodule, the second a most unusual case of multiple neuromas associated with multiple meningiomas, one of which proved to be a typical tumor of Type II, and in the third case a large parasagittal tumor in the right parieto-occipital region.

Case 4. (L. A. C. H. No. 3-534). A white man, aged 61, was admitted to the Hospital on June 6, 1938, with the history of many previous admissions with the clinical diagnosis of "asthma," although no definite cause for the persistent dyspnea could be found. Prior to admission, he had developed a psychosis of uncertain etiology and type. No neurologic or psychiatric examination had been made during his stay in the hospital. The patient's symptoms went unrelieved by usual doses of adrenalin and, although he appeared to be doing well, he suddenly died one month after admission. An autopsy (# 20-282) by Dr. L. J. Tragerman disclosed generalized arteriosclerosis, cardiac hypertrophy, severe pulmonary emphysema, gastric polyposus, sphenoid sinusitis and a Meckel's diverticulum. An incidental finding was a small friable tumor arising from the dura over the posterior surface of the left petrous bone just above the foramen magnum. It arose by a broad base and measured 2.2 x 2.2 by 1 cm. Microscopically, the solid portion of the tumor was reminiscent of the meningotheliomatous variety. Under higher magnifications, typical

strands of cells separating small sinusoids were clearly evident in the more vascular portions of the growth. In these areas, many small knot-like whorls were observed. A considerable portion of the stroma and of the larger blood vessels had undergone hyaline change. A few typical psammoma bodies were found. The tumor was evidently an *angioblastic meningothelioma*.

Case 5. *Case of Drs. C. W. Irish and J. M. Nielsen.* (L. A. C. H. No. 315-060). A white man, aged 31, died at the Hospital on Sept. 13, 1938, after a long lingering illness. He had been studied in a number of the larger hospitals and clinics in this country. His complaints, as recorded at the time of his last admission on Sept. 12, 1938, were bilateral tinnitus, progressing to deafness for 15 years, hoarseness, and weakness and wasting of the lower extremities for 9 years, an unstable gait for 8

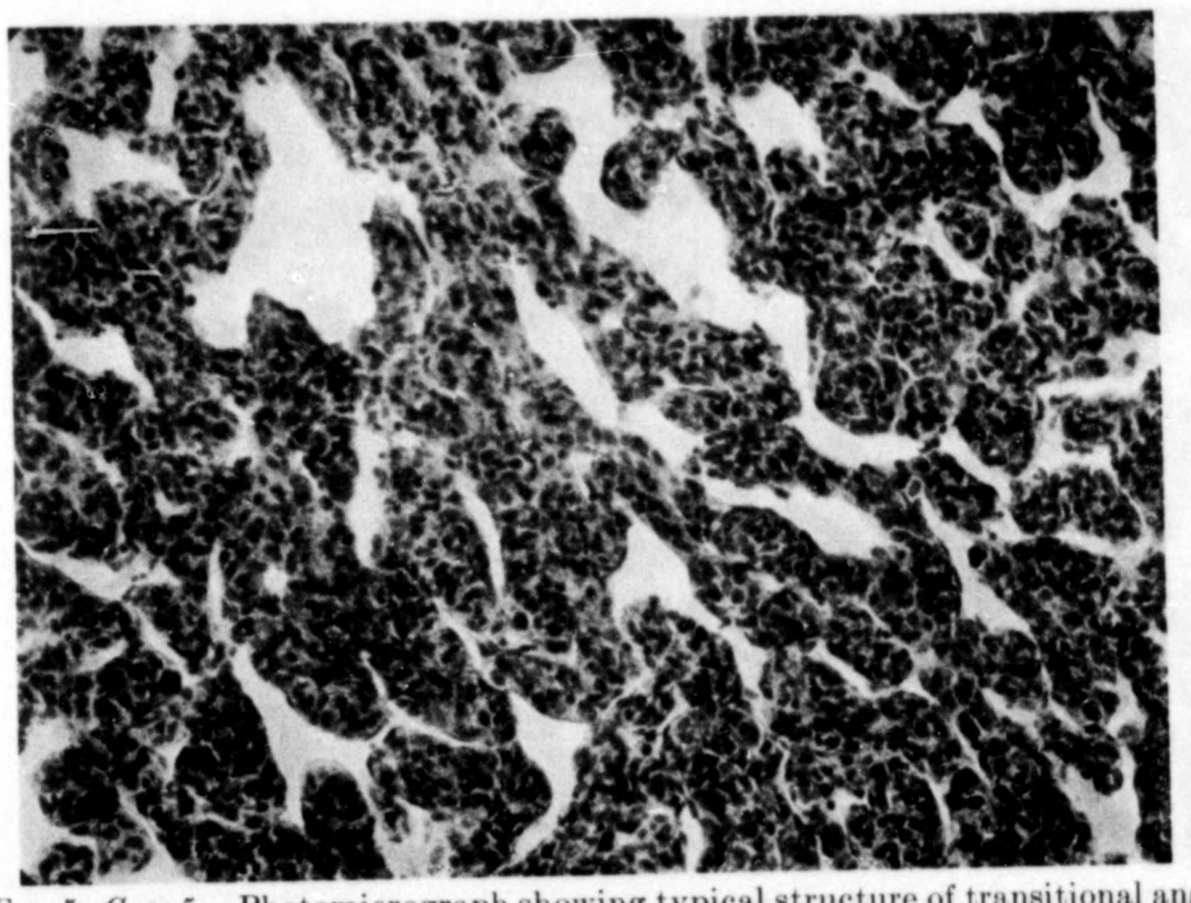

FIG. 5. *Case 5.* Photomicrograph showing typical structure of transitional angioblastic meningioma (Type II). H. & E., × 110.

years and pains in the legs for 2 years. His record disclosed the fact that, at the time of his first admission to the hospital on May 8, 1935, a biopsy of a tumor apparently arising from the left ulnar nerve disclosed a typical neurofibroma. Radiographs of the skull showed no erosion of the petrous ridge at this time. Since his discharge after second admission on Nov. 21, 1935, the patient had been confined to the Infirmary at the County Farm.

On examination at the time of his third admission, a bilateral nerve deafness, more advanced on the right, a husky voice, a prominent left eye, an apparent atrophy of the structures of the left face, left side of the tongue and soft palate and of both lower extremities, a bilateral foot drop with *pes cavus*, generally absent deep reflexes and a right Babinski were noted. Death came on Sept. 9, 1938, fifteen years after the onset of symptoms with signs of bronchopneumonia. At autopsy (#20-567) performed by Dr. C. P. Jensen, multiple tumors of the cranial nerve roots associated with multiple meningiomas were found. Many small flattened plaques of tumor

were scattered about on the inner surface of the dura. A large tumor, measuring 7.5 x 5.3 x 4 cm. compressed the right frontal lobe, while two smaller ones had embedded themselves in the medial aspect of the left frontal lobe. Sections from the large tumor disclosed a cellular growth, parts of which presented unmistakable evidences of the Type II variety of angioblastic meningioma (transitional *angioblastic meningioma*) (fig. 5). Bone (endostosis) was found in the part of the tumor adherent to the dura.

Case 6. *Case of Dr. C. W. Rand.* A housewife, aged 29, was first seen by Dr. Rand on Oct. 27, 1933, because of headaches associated with hallucinations of light in the left visual fields for 18 months, followed by a left homonymous hemianopia progressing to blindness in 7 months, and weakness in the left arm and leg for 10 days. Examination revealed a drowsy, blind woman with secondary optic atrophy of long standing and a spastic left hemiplegia with characteristic reflex changes. The spinal pressure proved to be 40 mm. (Hg) and radiographs of the skull revealed changes indicative of long continued increased intracranial pressure with thinning of the skull in the right occipital region. A hyperostosis measuring 4 x 4 x 1 cm. was noted in the right parieto-occipital (parasagittal) region after the head was shaved for surgery. A bruit was heard in the region of this swelling. At the first operative session, a bone flap was turned down and an underlying tumor was found to have penetrated the skull over an area of 3 x 4 cm. The tumor was enucleated at the second session under great technical difficulties because of profuse bleeding. Recovery was uneventful until early in 1939, when the headaches and vomiting recurred. Death came on Oct. 13, 1939, 7½ years after the onset of symptoms and 6 years after operation. An autopsy was not permitted. Microscopic examination showed the tumor (M-368) to be composed of strands of cells which separated fairly large sinusoids. Some portions of the tumor were more solid. It was a classical case of the II variant of Cushing and Eisenhardt (a *transitional angioblastic meningioma*).

Type III. Angioblastic Meningioma

This type of angioblastic tumor is presumed by Cushing and Eisenhardt[2] to lean still more definitely in the direction of the meningotheliomatous type of meningiomas, although in our experience *the arrangement of the cells is still not classical and typical of the usual case of meningothelial tumor.* This serves to distinguish it from the following group in which areas of such tissue are unmistakable. The true character of the tissue composing the tumor is to us uncertain. It certainly is entirely different from the tumor stroma of Type I and may be different from that of Type II. Nevertheless, in spite of variability in degree of its vascularity, this is a neoplastic entity, one not to be confused with any other. The tumor is a cellular one with many large blood spaces lined with tumor cells or what appears to be a single layer of endothelium. Connective tissue (in the form of reticulin) is found about these spaces and forms a network throughout the tumor. Definite tendencies toward malignancy are at times observed,—mitotic figures, irregularity in the size and shape of the nuclei, and giant cells. The tumor has been designated as an *angiosarcoma* (del Río-Hortega), *meningioma indifferentiale* (Globus) and *angioblastic menin-*

gioma (Bailey and Bucy, Cushing and Eisenhardt). Since we cannot be sure that the tumor tissue itself is identical with that forming the mesothelial variety, it seems just as well for the present to accept the nomenclature of Cushing and Eisenhardt and call it an *angioblastic meningioma*. The blood spaces are certainly a part of the neoplastic process.

Case 7. (Unknown Source). In this case the specimen was brought to the Laboratory under the name of Julius Memzer, but all efforts to trace it have thus far proven unavailing. The notes which accompanied the specimen indicate that the patient was a 50-year-old male and that the tumor had compromised his left frontal lobe. He had apparently died under uncertain circumstances for the autopsy had been performed by a coroner's surgeon. A section taken from the tumor showed the growth to be largely hyalinized but, in those areas where cellular detail was still evident, many blood vessels were evident. The unaltered tumor tissue resembled somewhat that of the meningotheliomatous variety and in these areas cells suggestive of those of mesenchyme were to be found. A few psammoma bodies were also present. The growth was quite obviously an *angioblastic meningioma*.

Case 8. *Case of Dr. L. J. Adelstein.* (L. A. C. H. No. 378-711). A Mexican man, aged 40, was admitted to the Hospital on Apr. 29, 1936, with the history of attacks of pain and distress in the abdomen for 17 years which seem to improve on ulcer management. For 5 months the pain had localized in the epigastrium and was associated with a band-like zone of increased sensitiveness about the upper abdomen. This was followed by numbness in the right leg and 4 months later by weakness in this leg. Weakness in the left leg had been present for a month, complete paraplegia and incontinence for 10 days. Examination disclosed a spastic paraplegia, more marked in the right leg, with increased deep reflexes and pathologic toe signs. A level of anesthesia was found at L-3, of hypesthesia at D-8 on the left and D-6 on the right. Lumbar puncture disclosed a yellow spinal fluid which coagulated on standing and contained an excess of cells and protein (Froin's syndrome). Radiographs of the spine failed to disclose any erosion of bone. An exploration by Dr. Adelstein on May 4, 1936, disclosed a meningioma at the level of D-5 attached to the inner surface of the dura at the level of D-5. When the patient was last seen on Mar. 24, 1939, he had no sensory residuals but the deep reflexes in both lower extremities were much exaggerated. The growth (# F-4194) measured 1.8 x 1.3 x 0.6 cm. On cut section it appeared to be very vascular. Microscopically, the tumor proved to be composed of variously-sized vascular channels, many of them thinwalled. The walls of some of the vessels had undergone hyaline degeneration. Between the vessels was a cellular tissue without signs of malignant change. No calcification was noted. The tumor proved to be a typical *angioblastic meningioma* (fig. 6).

Case 9. *Case of Dr. C. W. Rand.* (L. A. C. H. No. 5-411).* A white man aged 23, was admitted to the Hospital on June 22, 1932, with the history of headaches and

*This case is one of unusual interest in that the patient's father succumbed to the effects of a once cystic tumor of the cerebellum. Ten years before his admission to our hospital, he had been operated upon by Doctor Cushing and a large cerebellar cyst drained but no tumor tissue was found. He remained symptom-free for a period of six years. Then for four years there was a gradual recurrence of symptoms indicative of increased intracranial pressure and compression of the cerebellum. He suc-

dragging of the left foot for 3 years, intermittent numbness and weakness of the left leg and left side of the trunk for 2 years, and progressive weakness of the left arm and face since. On examination, bilaterally choked discs of 1-2 diopters elevation, weakness of the left lower extremity associated with exaggerated deep reflexes and pathologic toe signs, and early weakness and suggestive hypesthesia of the left upper extremity were noted. The patient was observed in a typical left-sided jacksonian seizure during the course of the examination. Radiographs of the head on June 23, 1932, showed a greatly enlarged sella turcica with erosion of the clinoid processes and signs of prolonged increased intracranial pressure. After four very stormy sessions on June 29, July 7, and 14, and Oct. 6, 1932, Dr. Rand removed a large left parasagittal tumor in the central region. When last heard from on June 9, 1939, the patient was still having left-sided jacksonian seizures from one to four

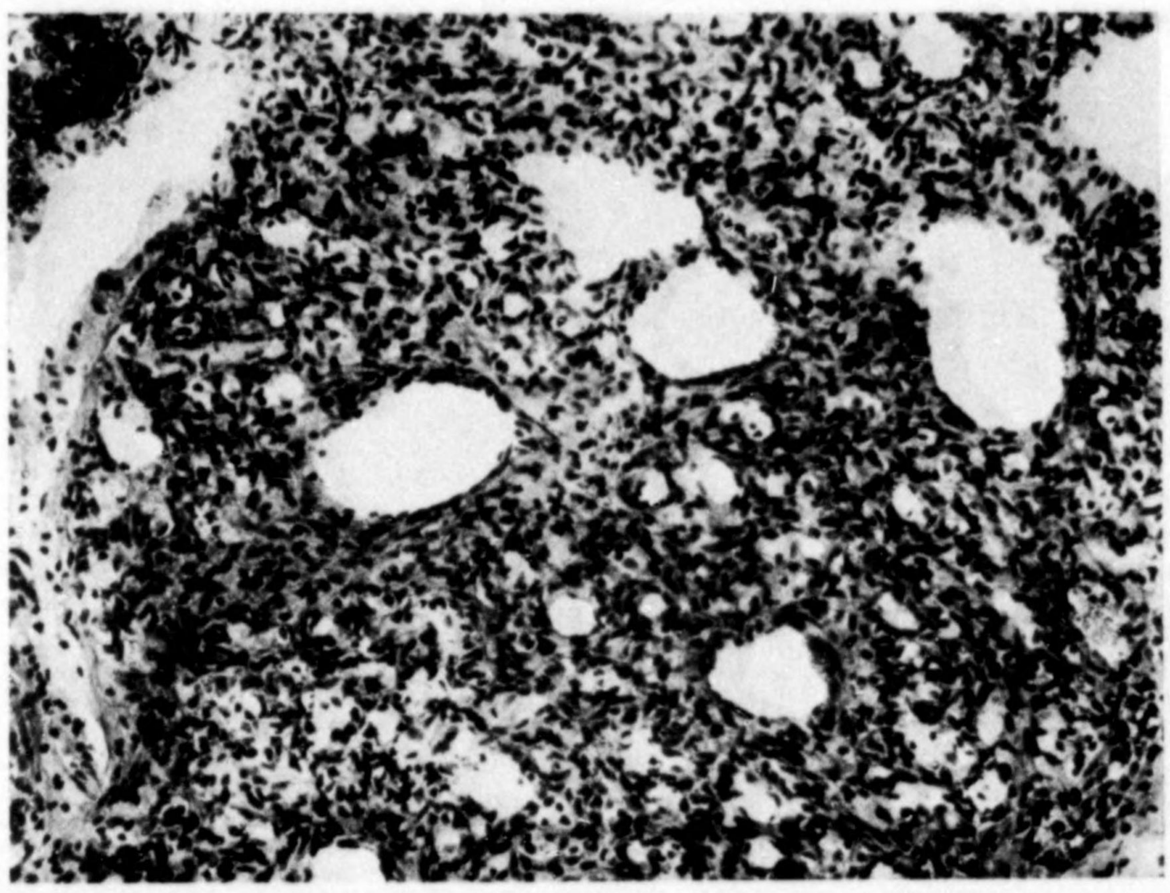

FIG. 6. *Case 9.* Photomicrograph showing structure of angioblastic meningioma (Type III). H. & E., × 110.

times a month. The tumor removed at operation measured 6.5 x 6.5 x 3.5 cms., being attached to the dura by a pedicle which measured 3.5 x 1 x 1 cms. The microscopic findings in this case were interesting. In some portions of the tumor, areas suggestive of meningotheliomatous tissue was found, in which large vascular spaces were present. In other areas the tissues were more typically mesenchymatous (in the sense of Bailey and Bucy) with many vascular spaces, somewhat like the lepto-

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cumbed following the removal of a large, very vascular tumor involving the right cerebellar lobe. When his presence in the hospital was made known to Doctor Cushing, he stated that a hemangioblastoma of the cerebellum had been suspected, this tumor being suggested by the presence of the large cyst. *A review of these slides after an interval of another ten years disclosed the tumor to be a fairly typical hemangioblastoma.*

meningeal angioblastomas. It is here grouped as an *angioblastic meningioma*, although it had some leanings toward the Type IV to be described shortly.

Case 10. In this case a pathologic specimen in the form of a small block of tissue was brought to the Cajal Laboratory for study by Dr. Carl W. Rand. It was impossible to obtain any history of the patient from the hospital in which he had been kept at the time of his death. The tumor had been removed surgically (it is presumed) but from what location could not be determined. On microscopic examination the tumor proved to be a typical *angioblastic meningioma*. In the diffusely cellular tissue was found many large, thin-walled blood vessels, typical of the angioblastic meningiomas. Hyalinization of the walls of the vessels and of the connective tissue stroma was of moderate degree. No calcification of any sort was observed.

Type IV. Combined Meningotheliomatous—Angioblastic Meningiomas

It is to this fourth type of angioblastic meningioma that the writers wish to direct special attention. It is composed in part of typical "meningothelial" tissue, circumscribed masses of which are to be found embedded in more cellular portions of what would otherwise be known as typical angioblastic meningiomas of Type II (II variant of Cushing and Eisenhardt) or of Type III (I variant of Cushing and Eisenhardt). It is quite obviously a mixed tumor, but in the writers' series is too common as to warrant inclusion in the above groups. The writers are unable to find any definite reference to this type of angioblatic meningioma. Other observers have apparently included it in the other groups. Three of thirteen cases studied in the Laboratory belonged to this "mixed" group.

Case 11. *Case of Dr. C. W. Olsen.* (L. A. C. H. No. 66-355). A white man, aged 43, was first admitted to the Hospital on June 26, 1929, with the complaint of attacks of numbness, pains and weakness of the left lower extremity for 11 months, having been constant for the past 6 weeks. These manifestations were considered to be due to lead poisoning. He was re-admitted to the Hospital on Feb. 6, 1931, with the complaint of persistence of numbness and weakness of the left side, and in addition, headaches, dizziness and blurring of vision. On the third admission on Feb. 7, 1934, the patient was found to be completely blind with a complete left hemiparesis and hemihypesthesia, with associated reflex changes. Advanced mental deterioration was also evident. Radiographs of the skull showed a deep, irregular sella turcica with erosion of both anterior and posterior clinoid processes. The vascular channels of the cranial vault were unusually prominent. What appeared to be calcification in the right central region was also observed. Death came on Mar. 1, 1934, nearly six years after the onset of symptoms. An autopsy (#11-244), performed by Dr. R. B. Haining, disclosed a large right parasagittal meningioma measuring 7.7 x 6.7 cm. in its greatest sectional diameters was found. There was an associated endostosis and exostosis with local erosion of the skull and enlargement of the regional diploic spaces. Microscopically, the tissue composing the tumor strongly resembled that of the meningotheliomatous variety, if the marked tendency of active cellular proliferation was discounted. Tumor giant cells were common. The vascular spaces were numerous and variable in size. In some areas where the spaces were small and in close proximity, the structure of the tissue was reminiscent of Type II, in others of Type III (fig. 7). This is probably a transitional type between

Type III and Type IV in which there is a combination of meningotheliomatous tissue and of angiomatous tissue particularly the Type II group.

Case 12. *Case of Drs. E. Ziskind and M. A. Glaser.* (C. L. H. No. 21-036). An adult white woman, aged 45, was admitted to the hospital on Apr. 28, 1934, with the history of left frontal headaches, dizziness and gradual diminution of vision for

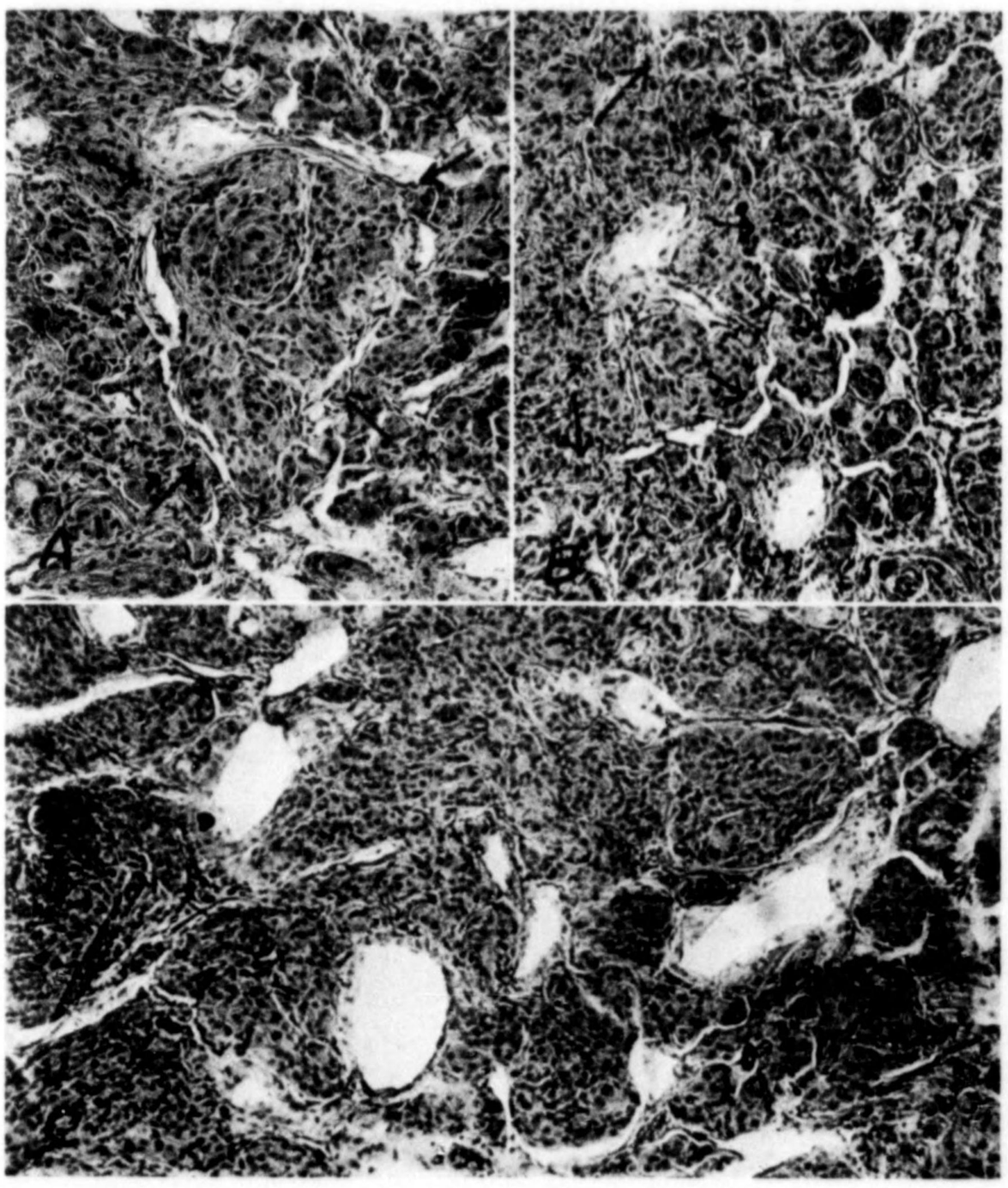

FIG. 7. *Case 11.* Combined type of angioblastic meningioma. Photomicrographs showing various types of tissue in tumor. *A*, island of typical meningotheliomatous tissue; *B*, tissue resembling that of transitional angioblastic meningioma (Type II); *C*, tissue resembling that of angioblastic meningioma (Type III). All H. & E., ×73.

2 years, and loss of memory, motor aphasia, weakness and numbness of the right leg for 2 months. On examination, dilatation of the right pupil, bilateral choked discs, a slight right facial weakness and exaggeration of all tendon reflexes were noted. Radiographs of the skull showed some rarefaction and increased vascularity near the vertex of the skull on the left side. An attempt was made by Dr. Glaser to remove a left postfrontal meningioma but the effort had to be abandoned because of severe hemorrhage and shock. The patient died the following day. At autopsy, a large

left parasagittal tumor (M-427) was found which measured 4.3 x 2.8 x 2.3 cm. Microscopic examination disclosed an atypical meningioma, one in which much typical meningotheliomatous tissue was evident, but which also had certain tendency to a

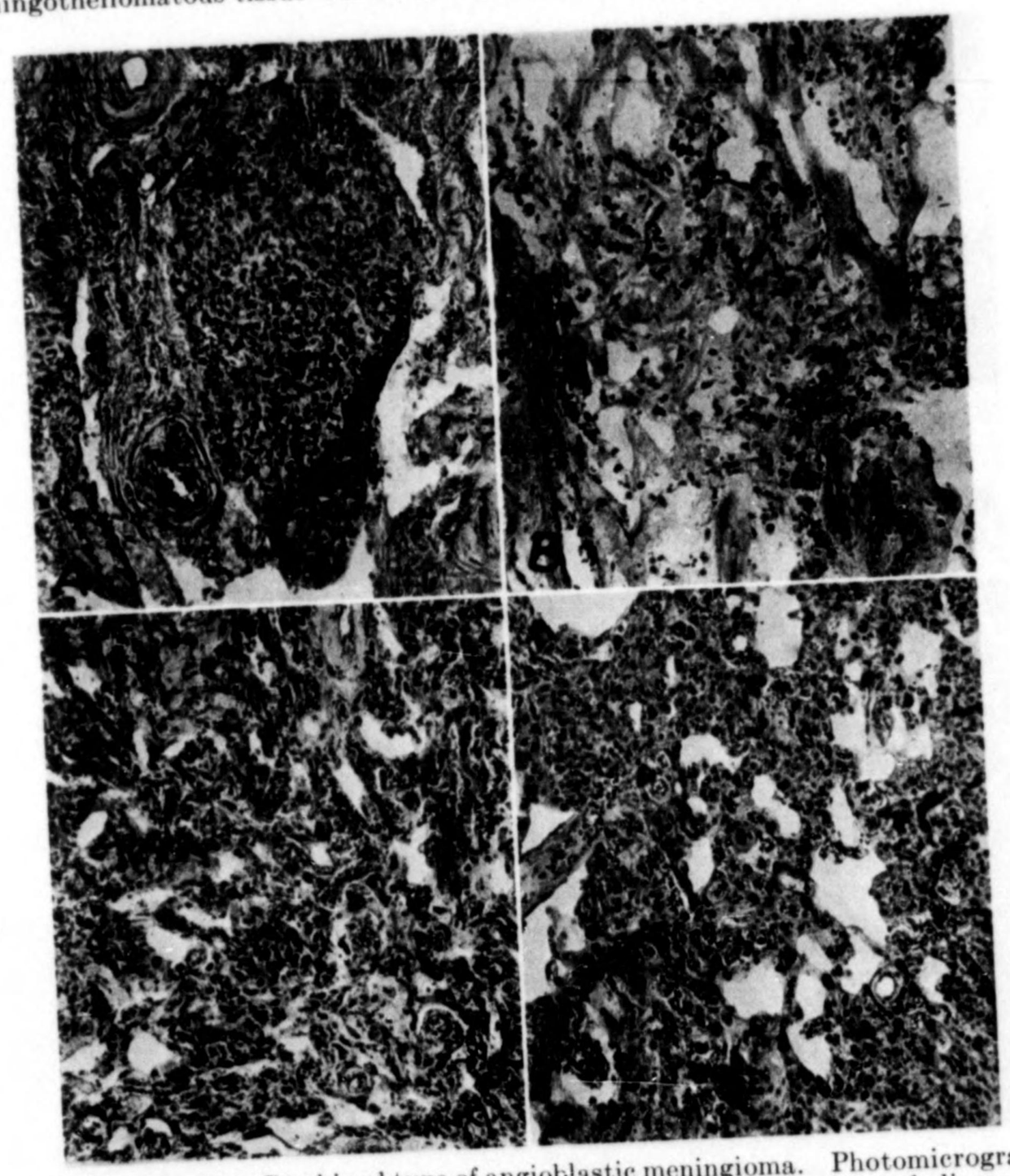

FIG. 8. *Case 13.* Combined type of angioblastic meningioma. Photomicrographs showing various types of tissue in tumor. *A*, island of typical meningotheliomatous tissue; *B*, tissue resembling that of Type I; *C*, tissue resembling that of Type II; *D*, tissue resembling that of Type III. All H. & E., ×73.

fibrous structure in some areas. The tumor was quite vascular and under higher magnifications definite structural arrangements typical of Type II were clearly evident. The tumor was obviously a "mixed" one, a definite combination of *meningothelial and angioblastic tissues*, questionably of fibroblastic elements as well.*

*This with another almost completely hyalinized tumor (Case 8) were the only two to show any tendency toward the fibroblastic or fibrous type of tumor and in these cases, the findings are by no means definite. A resurvey of the definitely fibroblastic type of meningiomas failed to disclose any with angioblastic leanings.

Case 13. (L. A. C. H. No. 226-856). A white man of 71 years was admitted to the Hospital on July 13, 1932, and died 6 days later. His complaints were those of dyspnea and weakness which had been present for 2 weeks. It was evident that the patient also had psychic aberrations. He proved to be an emaciated, pale, feeble old man who was evidently suffering from cardiac decompensation. Auricular fibrillation, râles at the bases of both lungs, and evidence of generalized arterial change were found on examination. After temporary improvement on digitalis therapy, the patient went down hill and succumbed with evidences of broncho-pneumonia. An autopsy (#8915), done by Dr. Lawrence Parsons, disclosed a miliary pulmonary tuberculosis, chronic myocardial disease and generalized arteriosclerosis. As an incidental finding, a small nodule of tumor arising from the inner surface of the dura over the left temporal lobe was also discovered. The tumor measured 2 cm. in its greatest cross sectional diameter and extended 1.5 cm. above the dural surface. Microscopically, the tumor was considered to be a meningotheliomatous variety basically, judging from the small amount of tissue which had not as yet undergone complete hyalinization. In some of these areas, more cellular than others, the arrangement of the tissue was suggestive of Type III. In others, strands of cells, quite actively proliferating were reminiscent of Type II, while in still other scattered areas the tissues resembled those of Type I angioblastoma (fig. 8). The tumor was considered to be a mixed one, *a meningotheliomatous meningioma with tendencies in the direction of both Types I and II.*

REPORTED CASES OF ANGIOBLASTIC MENINGIOMAS

In order to get the essential facts of the reported cases, now totaling forty-eight, a table (Table I) has been prepared. In surveying this table it is found that in the forty-six cases in which the age is stated, there was one case in the first decade (3 years), one in the second, seven in the third, ten in the fourth, fourteen in the fifth, eight in the sixth, four in the seventh, and one in the eighth (71). As far as sex was concerned twenty-one were females, and twenty-seven were males, a reverse of the usual sex ratio in meningiomas of all types of 60 females:40 males as found by Cushing and Eisenhardt[2]. As for location, a schematic drawing adapted from Cushing has been prepared, the various lesions being indicated as near as the reported size and situation would permit (fig. 9). The survival period varied so widely that no conclusions can be drawn from these figures. In some cases it has not been possible to establish the exact type, for obviously some of the mixed types have not been considered by Cushing and Eisenhardt.*

THE ANGIOBLASTIC MENINGIOMAS: THEIR GROSS CHARACTERISTICS AND LIFE HISTORY

It has been established beyond all question that the angioblastic group of tumors constitute a special variety, a constellation all its own within the

* Probably with some wisdom. In a letter to the senior author about the problem of classification of the meningiomas, Doctor Cushing wrote: "Don't bear down too heavily on the eight varieties we showed on page 31 (of the monograph). We might

larger system of the meningiomas. With the possible exception of Type III (Cushing and Eisenhardt's I variant), which seemed to have a predilection for the peritorcular region in Cushing's series, this group of tumors may grow anywhere that any other meningioma may arise, including the spinal canal. They are encapsulated tumors, at times lobulated but often smooth surfaced, which distinguishes them from those warty-surfaced growths which are made up of myriads of whorls.

Perhaps their most distinguishing characteristic *in situ* is the extreme degree of vascularity, an important fact for the surgeon which Auvray discovered, perhaps to his consternation, over fifty years ago. This "internal" vascularity does not necessarily mean that the vascular connections with the brain or the dural sinuses are any more marked than in other types of meningioma. At least, enlargement of the diploic spaces so characteristic of other vertex meningiomas is not often marked in the angioblastic variety, possibly due to their shorter clinical course. This "internal" vascularity is often visible in the gross specimen on cut section when, with the aid of a hand lens, the porous or spongy texture of the tissue becomes obvious and should suggest the true nature of the tumor.

Perhaps the most striking growth tendencies of the tumor may be either *regressive* in the form of extensive hyalinization or *progressive* in its frequent tendency to malignant degeneration. *Hyalinization* may render the growth completely inert, resulting in shrinkage of the mass, as was observed in one of our cases (Case 1). When the sections were first studied so little of the tissue remained unaltered that no diagnosis could be made at the time. Only when a restudy was made of the series of meningiomas did its relationship to the angioblastic group become fully apparent. From our own experience, the angioblastic meningiomas show the greatest tendency to hyalinization, although, to be sure, this change is found in other types. The process seems to affect the walls of the blood vessels and the connective tissue stroma of the tumor tissue.

Malignant degeneration is also prone to occur in any of the four types of angioblastic meningiomas. In our experience this change has never been extensive or profound, although in patients with partial resections and therefore with longer survival periods, this change may come to involve the entire mass. It has been limited in our series to Types II, III and IV. It is usually manifested by increased size and irregularity of the nuclei and the production of tumor giant cells, at times also by the presence of mitotic figures. As the process spreads, the cell strands (Types II and IV) or masses (Types III and IV) become generally active and at times the

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have made a dozen more." There are limits to this matter of classification of tumors; we have added a fourth group only because their numbers and structural variations (and their possible significance) seems to indicate this move.

TABLE I—*Concluded*

NUMBER	CASE	AGE	SEX	LOCATION OF TUMOR	SIZE	SURVIVAL PERIOD	L OR D	TYPE
				Cushing and Eisenhardt—*Continued*				
20	60	61	M	Right peritorcular	65 gm.	5 yrs.	D	II
21	94	57	F	Right middle ridge—equal in each fossa (right sylvian fissure)	50 gm.		D	II
22	97	42	F	Right coronal (convexity)	80 gm.	7 yrs.	D	II
23	115	39	F	Right subtentorial	?	4 yrs.	D	I
24	134	62	F	Right central parasagittal	13 gm.	13 yrs.	L	II
25	146	48	M	Left coronal (convexity)	57 gm.	2½ yrs.	D	II
26	149	40	M	Spinal T-10	2 cm.	12 yrs.	L	I
27	154	39	M	Right pterion	80 gm.	1 yr.	D	II
28	196	12	M	Subtentorial	80 gm.	10 yrs.	L	I
29	211	21	M	Right peritorcular	60 gm.	5 yrs.	D	III
30	232	28	M	Right peritorcular	120 gm.	2 yrs.	D	III
31	255	50	M	Right parietal convexity	38.5 gm.	4 yrs.	D	II
32	260	40	M	Left subtentorial	80 gm.	4 yrs.	D	I
33	269	31	M	Right peritorcular	150 gm.	1 yr.	D	III
34	293	31	M	Right coronal (convexity)	75 gm.	3 yrs.	D	II
35	310	45	M	Left pterion (global)	100 gm.	5 yrs.	L	II
				Courville and Abbott				
36	1	60	F	Left central parasagittal	3.4 x 3 x 3 cm.	32 yrs.(?)	D	I
37	2	57	M	Left central parasagittal	4.1 x 3.2 x 2.4 cm.	8 yrs.	L	I
38	3	56	F	Right pterion	7.5 x 5 cm.	2 yrs.	D	I
39	4	61	M	Left subtentorial	2.2 x 2.2 x 1 cm.	?	D	II
40	5	31	M	Multiple tumors, angioblastic in left frontal region	7.5 x 4 x 5.3 cm.	15 yrs.	D	II
41	6	29	F	Right parieto-occipital (? peritorcular)	4 x 4 cm.	7½ yrs.	D	II
42	7	50	M	Left frontal lobe	?	?	D	III
43	8	23	M	Left parasagittal (central)	6.5 x 6.5 x 3.5 cm.	10½ yrs.	L	III
44	9	40	M	Spinal T-5	1.8 x 1.3 x 0.6 cm.	4½ yrs.	L	III
45	10	?	M	(Supratentorial)	?	?	?	III
46	11	43	M	Right parasagittal	7.7 x 6.7 cm.	6 yrs.	D	IV
47	12	71	M	Left temporal lobe	2 x 2 x 1.5 cm.	?	D	IV
48	13		F	Left parasagittal (coronal)	4.3 x 2.8 x 2.3 cm.	2 yrs.	D	IV

TABLE I

Reported Cases of Angioblastic Meningiomas

NUMBER	CASE	AGE	SEX	LOCATION OF TUMOR	SIZE	SURVIVAL PERIOD	L OR D	TYPE
Bailey, Cushing and Eisenhardt								
1	1	44	F	Right peritorcular (3 reoccurrences)	50 gm. 404 gm. 220 gm.	5 yrs.	D	III
2	2	34	F	Right temporal fossa attached to tentorium	181 gm.	2½ yrs.	D	I
3	3	30	F	Right peritorcular cerebellar and occipital	Massive (at autopsy)	4 yrs.	D	II
Bailey								
4		47	M	Right temporal fossa	150 gm.	9 mo.	D	II
Bergstrand and Olivecrona								
5	1	47	F	Left parasagittal "middle third"	?	2½ yrs.+	L	I
6	2	3	F	Left parasagittal "middle third"	?	1½ yrs.+	L	I
7	3	54	F	Left ant., middle and post. fossae	"Massive"	5 yrs.	D	III(?)
8	4	22	F	Left sylvian fissure	"Tangerine orange"	2½ yrs.	D	III(?)
Bailey and Bucy								
9		27	M	Left frontal lobe	6.5 x 5.5 x 5.5 cm.	1 yr.+	L	I
Wolf and Cowen								
10	1	36	M	Right parieto-occipital	6.5 cm.	12 yrs.	D	I
11	2	49	M	Right paracentral	3.5 cm.	3 yrs.	D	I
12	3	25	F	Right pterion	47 gm.	5 yrs.+	L	IV(?)
13	4	46	M	Left frontal	?	2 yrs.	D	I
14	5	50	F	Left frontal	5 cm.	11 mo.+	L	IV(?)
15	6	58	F	Left frontal (parasagittal)	4 cm.	1 yr.+	L	IV(?)
Cushing and Eisenhardt								
16	22	44	F	Right peritorcular (3 recurrences — massive)	40 gm. 404 gm.	3 yrs.	D	III
17	23	30	F	Spinal C-7	1.9 cm.	7 yrs.	D	I
18	35	33	M	Right subtentorial	35 gm.	22 yrs.	L	I
19	57	43	M	Left central parasagittal	83 gm.	9 mo.	D	II

TABLE I—*Concluded*

NUMBER	CASE	AGE	SEX	LOCATION OF TUMOR	SIZE	SURVIVAL PERIOD	L OR D	TYPE
				Cushing and Eisenhardt—*Continued*				
20	60	61	M	Right peritorcular	65 gm.	5 yrs.	D	II
21	94	57	F	Right middle ridge—equal in each fossa (right sylvian fissure)	50 gm.		D	II
22	97	42	F	Right coronal (convexity)	80 gm.	7 yrs.	D	II
23	115	39	F	Right subtentorial	?	4 yrs.	D	I
24	134	62	F	Right central parasagittal	13 gm.	13 yrs.	L	II
25	146	48	M	Left coronal (convexity)	57 gm.	2½ yrs.	D	II
26	149	40	M	Spinal T-10	2 cm.	12 yrs.	L	I
27	154	39	M	Right pterion	80 gm.	1 yr.	D	II
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29	211	21	M	Right peritorcular	60 gm.	5 yrs.	D	III
30	232	28	M	Right peritorcular	120 gm.	2 yrs.	D	III
31	255	50	M	Right parietal convexity	38.5 gm.	4 yrs.	D	II
32	260	40	M	Left subtentorial	80 gm.	4 yrs.	D	I
33	269	31	M	Right peritorcular	150 gm.	1 yr.	D	III
34	293	31	M	Right coronal (convexity)	75 gm.	3 yrs.	D	II
35	310	45	M	Left pterion (global)	100 gm.	5 yrs.	L	II
				Courville and Abbott				
36	1	60	F	Left central parasagittal	3.4 x 3 x 3 cm.	32 yrs. (?)	D	I
37	2	57	M	Left central parasagittal	4.1 x 3.2 x 2.4 cm.	8 yrs.	L	I
38	3	56	F	Right pterion	7.5 x 5 cm.	2 yrs.	D	I
39	4	61	M	Left subtentorial	2.2 x 2.2 x 1 cm.	?	D	II
40	5	31	M	Multiple tumors, angioblastic in left frontal region	7.5 x 4 x 5.3 cm.	15 yrs.	D	II
41	6	29	F	Right parieto-occipital (? peritorcular)	4 x 4 cm.	7½ yrs.	D	II
42	7	50	M	Left frontal lobe	?	?	D	III
43	8	23	M	Left parasagittal (central)	6.5 x 6.5 x 3.5 cm.	10½ yrs.	L	III
44	9	40	M	Spinal T-5	1.8 x 1.3 x 0.6 cm.	4½ yrs.	L	III
45	10	?	M	(Supratentorial)	?	?	?	III
46	11	43	M	Right parasagittal	7.7 x 6.7 cm.	6 yrs.	D	IV
47	12	71	M	Left temporal lobe	2 x 2 x 1.5 cm.	?	D	IV
48	13		F	Left parasagittal (coronal)	4.3 x 2.8 x 2.3 cm.	2 yrs.	D	IV

original character of the tumor may be difficult to determine (as in our Case 13).

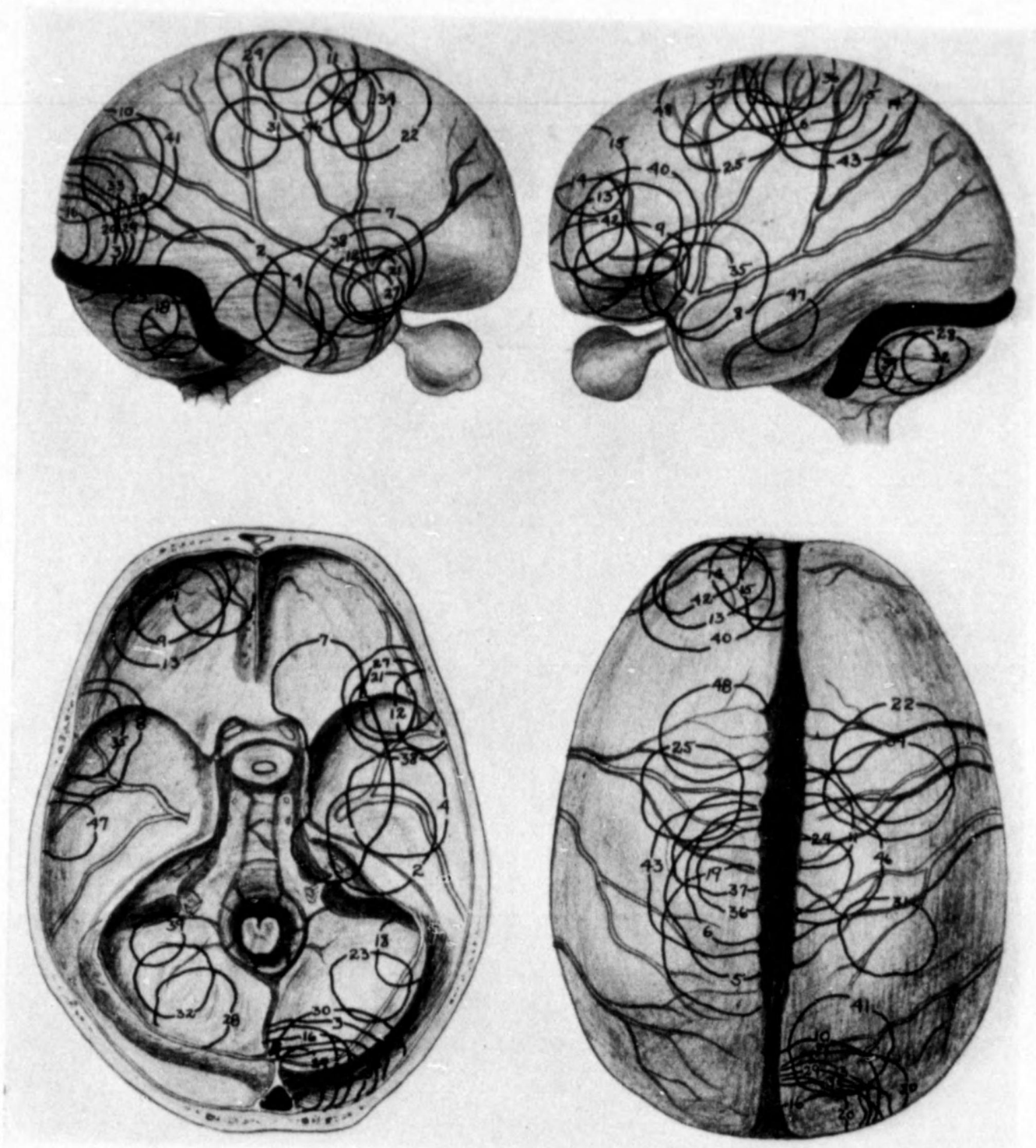


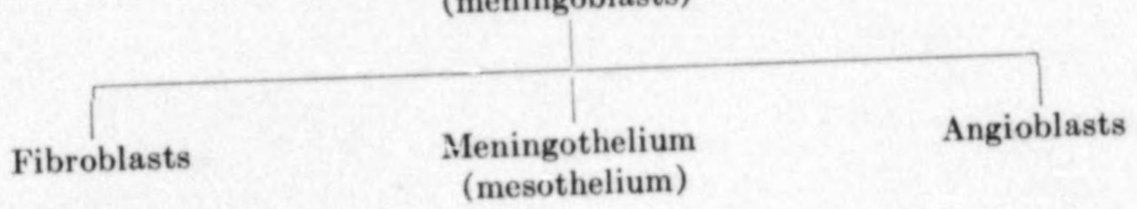
FIG. 9. Diagrams (after Cushing) showing approximate areas of attachment of forty-five reported cases of intracranial angioblastic meningiomas. Three intraspinal cases, two of Cushing and Eisenhardt (Cases 17 and 26 of Table), C-7 and T-10, and of one of the authors', T-5, are not included.

ON THE CLASSIFICATION OF MENINGIOMAS IN GENERAL AND THE ANGIOBLASTIC VARIETY IN PARTICULAR

If history has anything to teach about the group of tumors now generally known as meningiomas, it is that, while the tumors in this group may be grossly similar as far as their morphology, encapsulation and common points of origin are concerned, their structure may vary within wide limits.

This becomes obvious even to the casual reader of writings of German, French and English pathologists of the latter decades of the Nineteenth Century who tried desperately to make these variations fit into the current scheme of "sarcomas." Some were obviously fibrous, others were made up of clusters of rounded cells and still others were very vascular. This much was to be said for their attempts at classification that, in spite of this variation in structural appearances, these tumors were included in the same general group of dural tumors.

When the behavior of tumors began to be interpreted in the light of cellular activity, the question naturally arose as to reason for this difference in cell type. A number of attempts have been made to account for this variation on a histogenetic basis. In their original discussion on angioblastomas, Bailey, Cushing and Eisenhardt[1] proposed the following scheme:



Interpreted in the light of cellular activity in meningeal tumors, one might expect to find certain tumors whose cellular elements might resemble the primitive mesenchyme and in whose evolution evidences of malignancy might be expected as well as deviations in the direction of fibroblasts, mesothelial cells or angioblasts. Indeed, Bailey and Bucy[16] described a meningeal tumor whose structure was not unlike embryonal mesenchyme, but which presented no evidence of malignancy and no stated tendency to deviate in the direction of mesothelium or angioblasts, but possibly in the direction of fibroblasts in its tendency to form reticulin. These tumors must be rare; Cushing and Eisenhardt found none of them in a series of 313 cases. The authors have found no example in now over 100 cases of meningiomas in their series.

One other important fact seems to be clearly established to date by the various students of this interesting tumor, and that is that mixed tumors are fairly common. While recognized before, del Rio-Hortega stressed this point and designated those growths containing both fibrous and meningothelial tissues as "exotelioma diffuso y laminar." Globus and Cushing and Eisenhardt also recognize the possibility although Bailey and Bucy do not seem to do so. The writers found these transitional or combined type of tumors common enough (22 per cent) to warrant making a separate group of them. It should be said that there is considerable variability in the amounts of the two tissues in the various tumors in this group.

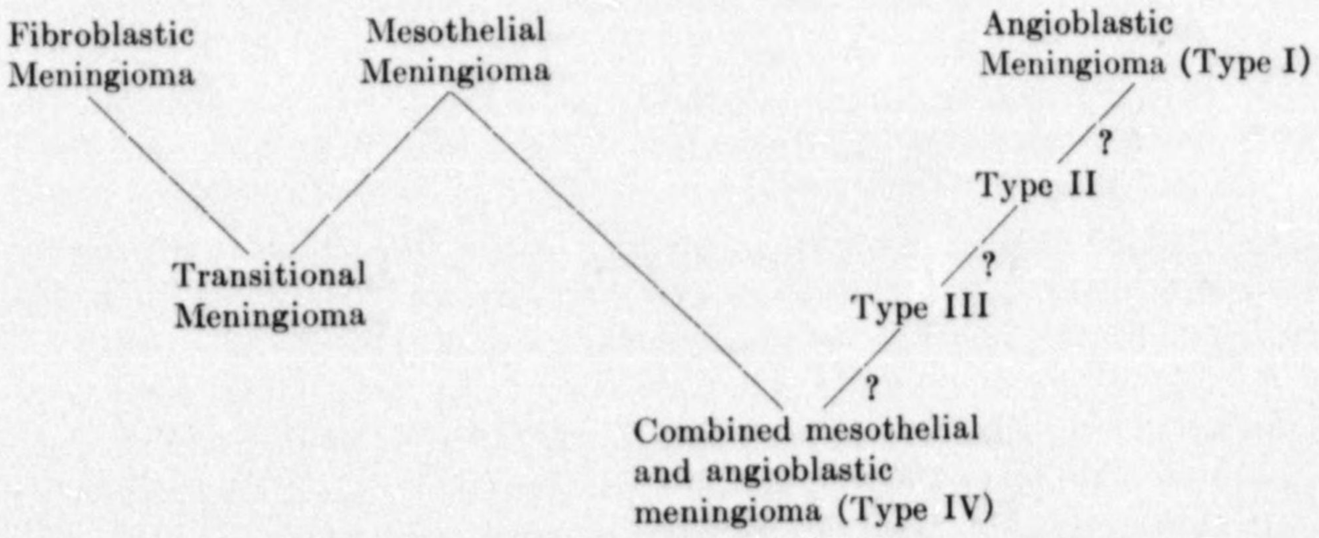
As applied to the problem of angioblastic tumors, the matter of mixed

tumors is also of interest. The purest type of angioblastic meningioma is Type I (III variant of Cushing and Eisenhardt) which is a neoplastic entity, one which is closely related structurally with the cerebellar hemangioblastomas. Type II (II variant of Cushing and Eisenhardt) is less pure although in clear-cut examples the arrangement of cell strands to the capillary spaces is very characteristic. In our examples a considerable portion of the tissue was suggestive somewhat of the mesotheliomatous variety. Although not identical with it in Type II (I variant), it seems as though one might be dealing with an atypical mesotheliomatous meningioma with a greater or less tendency to form capillary spaces.

Of even greater significance was the discovery of true "mixed" tumors in this group. In three of our thirteen cases, unmistakable areas of true mesothelial tissue was found in angioblastic tumors of Types I and II. In some cases the mesothelial elements were predominant, in others the angioblastic. This observation seems to indicate that either certain "parent" cells (what cells in the tumor are parent cells?) are bipotential or that two types of cells, pursuing independently their neoplastic course, grow side by side.

Two facts seem to be pertinent: (1) that no clear-cut case of a mixture of angioblastic tissue and fibroblastic tissue has been reported: (in two of our cases there were some slight propensities in this direction although the advanced degree of hyalinization of the tumors made exact interpretation difficult); (2) that with the possible exception of the Type III, no evidence whatever of definite mesenchymatous tissue has been found.

As a result of these findings it would seem as though there is tendency for a combination of the angioblastic and mesotheliomatous types of meningiomas on one hand and the mesotheliomatous and fibroblastic type on the other. Disregarding any possible histogenetic significance for the time being, the following schema seems to be applicable.



In this schema, the writers have not included the so-called mesenchymal meningioma because they have no personal experience with it as a pure lesion and have seen no transitional forms. For reasons stated in a

previous paper "On the Classification of the Meningiomas"[16] we do not include diffuse tumors or primary melanoblastomas (not a meningioma in any sense), psammomas (psammoma bodies are found in all varieties though some are more prone to form them), osteomas (an evidence of proliferation or retrogression, not of neoplastic activity) or chondromas (authors have had no personal experience, possibly a true type of meningioma).

SUMMARY AND CONCLUSIONS

1. The group of meningiomas which have a special propensity to form new blood channels (angioblastic meningiomas) form a small constellation of their own. Three classic types have been described by Cushing and Eisenhardt, to which the writers add a fourth "mixed" group.

2. This type of tumor has been recognized for many years having been variously designated as an angiosarcoma, plexiform angiosarcoma, perithelioma, hemangioendothelioma, cylindroma, plexiform endothelioma or hemangioendothelioma. Not only has the vascular component been early appreciated, but also that these vessels were new formed and a constituent part of the tumor was also recognized by pathologists.

3. A series of thirty-five verified cases have been collected from the literature to which the writers add thirteen cases of their own which have been studied from a pathologic standpoint.

4. In addition to the typical (hem-)angioblastic tumor which corresponds closely to the hemangioblastomas of the cerebellar cortex (Type I of the writers), the more cellular transitional angioblastoma (Type II) and the angioblastic meningioma (Type III), another type in which an admixture of characteristic syncytial (or meningothelial) tissue with tissue resembling that of Type I or Type II is present, is also described (Type IV). This "mixed" tumor corresponds to the combined type of meningioma in which both syncytial (meningothelial) and fibrous elements are found.

5. The angioblastic tumors are prone to undergo hyaline degeneration and show signs of malignant change. Calcification is found in the form of calcareous "dust" (in the larger hyalinized blood vessels), small calcospherites and typical psammoma bodies. Bone formation, in a neoplastic sense, does not occur although an endostosis in response to a disturbance of circulation in the overlying skull may take place.

6. The significance of the cellular elements in these various types of angioblastic tumors is of interest and importance in understanding their character. Whether Types I, II and III are to be arranged in a progressive order as transitional forms in a series is open to some question. It is also uncertain whether or not the cellular tissue between the new formed vascular channels is to be considered as "meningothelial" in character.

The reasons for this doubt are the uncertainty of transition between the three types, the greater tendency to malignant change in the angioblastic as compared to the meningotheliomatous variety, the greater tendency of the angioblastic cells to form reticulin, and finally the occurrence of isolated islands of typical syncytial or meningothelial tissue in Type II or Type III tumors ("mixed" tumors, Type IV) which show no evidences of transition between the two types of tissue. The angioblastic tumor is more closely related to the meningothelial than to the fibroblastic type as seems to be shown in the absence of definite examples of fibroblastic meningiomas with angioblastic leanings or of "mixed" angioblastic and fibroblastic types. From the standpoint of structural analysis, the syncytial or meningothelial type of meningioma lies between the angioblastic and the fibroblastic types.

7. Their shorter survival period, their marked tendency to recur, as well as common microscopic evidences of accelerated neobiologic activities indicate that the angioblastic meningioma is a potentially more dangerous type of tumor than is the average syncytial, fibrous or combined type of meningioma. This constitutes a clinical challenge to early diagnosis and appropriate surgical attack. The pointing out of important facts, such as these which prove to be of help to the clinician and surgeon in service to the patient, tends to restore Pathology once more to its place as a humanitarian science. Whether he fully appreciated it or not, this was one of the great, if indirect, achievements of the life and work of Dr. Harvey Cushing.

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NEURO-GLIOGENIC TUMORS OF THE CENTRAL NERVOUS SYSTEM*

REPORT OF TWO ADDITIONAL CASES OF GANGLIOGLIOMA OF THE BRAIN

CYRIL B. COURVILLE, M.D. AND FRANK M. ANDERSON, M.D.

The occurrence of nerve cell-containing tumors arising from the peripheral nervous system, particularly that part of it known as the sympathetic system, has long been recognized. Since these tumors are composed of both nerve cells and fibers, they have been called *ganglioneuromas*. A group of ganglion cell tumors of the central nervous system then came to be distinguished. In this group, the neoplastic rôle played by the nerve fibers was recognized to be relatively small. As time went on, it was further discovered that, in addition to the ganglion cells, other elements, evidently of glial origin, were also present. Some of the German writers then began to speak of these tumors as *ganglioglioneuromas*, a term which is an unfortunate one, if for no other reason than for the fact that the two elements of the term referable to the neuron are separated by one designating the glial derivatives. In an effort to reduce its terminology to its simplest elements, the senior author of this study, following the suggestion of Ewing, used the term *ganglioglioma* as descriptive of three cases previously reported by him. The reasons that seem to make advisable the continued use of the term will be made clear in subsequent sections of this study.

The newgrowth with which we are now to deal is a benign, granular tumor of the glioma group, which shows a special predilection for the floor and perhaps the immediately adjacent lateral walls of the third ventricle, but which may also arise from the cortex or subcortical regions of the cerebrum or cerebellum, the pons, medulla and cervical spinal cord. It is usually sharply delineated from the enveloping brain tissue except in a few cases in which it appears as a neoplastic transformation of the cerebellar and, more rarely, of the cerebral cortex as well. It may contain a few small cysts, or a single moderate sized one, or may present itself as a mural nodule in the walls of a large cyst which may reach enormous proportions. As further evidence of its slow evolution, is the presence in so many cases of calcospherites in the smaller blood vessels. It is now quite generally agreed that both nerve (or 'ganglion') cells and glial cells, play

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a part in the elaboration of the tumor. It is, therefore, a *mixed* tumor with two distinct cellular elements contributing to its enlargement, and, because of this fact, occupies a unique position among the other tumors of the glioma group. While its architecture and cellular details are quite characteristic, it is quite certain that most of these tumors are being passed by unrecognized. A resurvey of the entire problem for this reason is very much in order.

In this further study of this interesting tumor, it is the writers' purpose to report two additional cases in which material for the histologic studies was obtained in the course of surgical explorations. Unfortunately, one of the patients died of surgical shock and postoperative hemorrhage, the tumor having been completely removed as proven by autopsy. The second patient still survives apparently quite well, though completely blind. With these two cases as a point of departure, some of the questions which still seem to confuse the issue will be given consideration.

REPORT OF CASES

Case 1. *Frontal and parietal headaches with nausea and vomiting for six years in an eight-year-old boy. Obliteration of the posterior horn of the right lateral ventricle demonstrated by ventriculography. Mural nodule removed from large gliomatous cyst in the right parietal region. Death one day after the operation. Autopsy. Characteristic ganglioglioma disclosed by histologic study.*

(Los Angeles County Hospital No. 508–237.) On July 21, 1936, a conscious and rational, but rather irritable white boy of eight years was admitted to the hospital for diagnosis and treatment with a history of bilateral frontoparietal headaches associated with dizziness and nausea and vomiting which began at the age of two. At first, the headaches occurred relatively infrequently, but were inclined to persist for several days at a time. As the years passed, the headaches became more severe, but, peculiarly enough, in the two years before admission to the hospital, had been complained of less often and did not seem to be as marked as before. During the year prior to admission, the boy had a more or less constant anorexia, leading to nausea and vomiting when the headaches did become accentuated. For seven months before admission, the patient had complained of pain in the left knee and calf on sitting down, a discomfort which came on during one of his bouts of headache, nausea, and vomiting. For several years it had been noticed that he had been nervous and irritable and preferred to play with girls rather than boys because he was easily hurt and noise bothered him.

The past personal and family history were entirely irrelevant.

When seen for the first time in the hospital, the boy complained of frontal headache which he localized over the right side of the head. The right frontal and parietal regions seemed more prominent than the left, although the entire head seemed larger than normal. The percussion note over the skull seemed somewhat high pitched on this side. The pupils were equal in size and reacted normally to light and convergence. A bilateral papilledema of two diopters elevation was found on ophthalmoscopic examination. Some weakness on voluntary movement of the left lower face, arm, and leg was also found, with pathologic toe signs on this side. The deep reflexes were not notably altered. The abdominal reflexes were likewise active and equal on the two sides. The boy was unsteady on his feet, walking with a wide base

and deviating more toward the right side. A moderate degree of pastpointing to the left was evident. Otherwise no other signs suggestive of cerebellar disease could be elicited.

Radiographs of the skull taken on July 22, 1936, disclosed an irregular deposit of calcium salts in the posterior portion of the cranial vault on the right side. The convolutional markings of the inner table of the skull were unduly prominent, suggesting an increased intracranial pressure. No other significant alterations were noted.

In order to localize the lesion more definitely, Dr. H. G. Crockett injected air into the left lateral ventricle on July 30, 1936, following which further radiographic studies were made. The entire ventricular system was found to be displaced to the

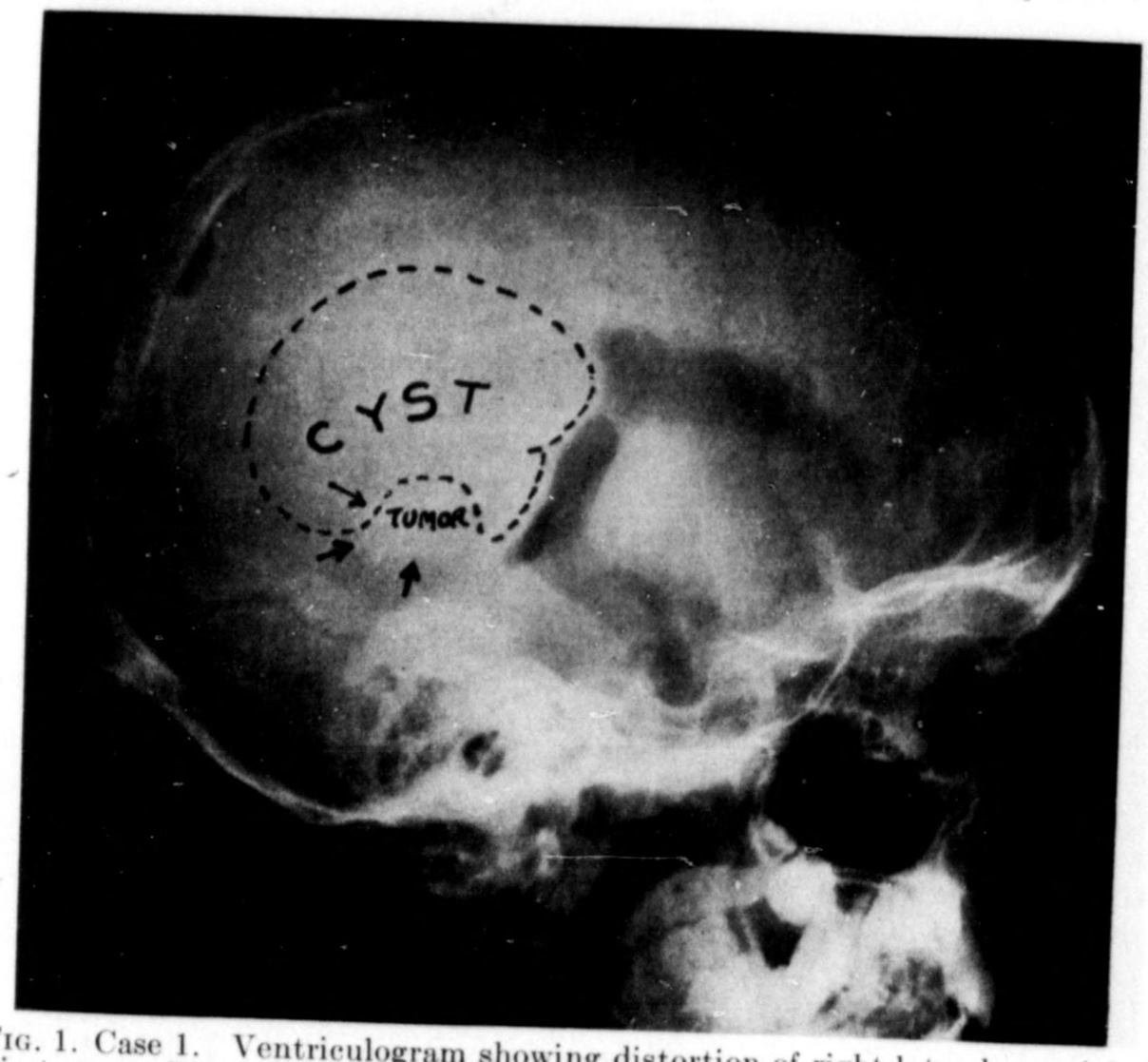

FIG. 1. Case 1. Ventriculogram showing distortion of right lateral ventricle by cystic tumor. Flecks of calcium can be seen (arrows) at margin of nural module.

left. The posterior horn of the right lateral ventricle was obliterated and the vestibule of the ventricle displaced forward (fig. 1), evidently the result of a calcified tumor in the right parieto-occipital region.

On August 3, 1936, a right parieto-occipital exploratory operation was performed under avertin and local anesthesia by Dr. George H. Patterson, senior attending neurosurgeon. A large cyst, apparently multilocular, was tapped with a ventricular needle and approximately 200 cc. of xanthochromic fluid was evacuated. This cyst was opened and a small mural nodule about five centimeters in diameter was removed together with a portion of the underlying brain (fig. 2).

The patient failed to recover from the shock of the operation and died the following morning, twenty-two hours after surgery. An autopsy was performed by Dr. Frank

R. Webb, Coroner's Surgeon, on August 5, 1941. No residual tumor tissue was found but the cavity from which the tumor had been removed was filled with blood clot. The postoperative hemorrhage had apparently ruptured into the right lateral ventricle and filled the ventricular system with blood.

A histologic study was made of the tumor tissue removed at operation and submitted to the Cajal Laboratory (F-6354) for examination.

Routine sections through a large mass of the tumor showed it to be quite sharply delineated from the enveloping brain, as indicated on one side where a fragment of nervous tissue was still adherent. The *architecture* of the tumor was characterized by the presence of a loose stroma with a neurinomatous arrangement ("neurinoma centrale"), with imperfect pseudopalisading in which large irregular cells with clear vesicular nuclei were embedded, together with other smaller cells of variable nature (fig. 3, *A*). The tumor tissue as a whole was not as cellular as some examples of the

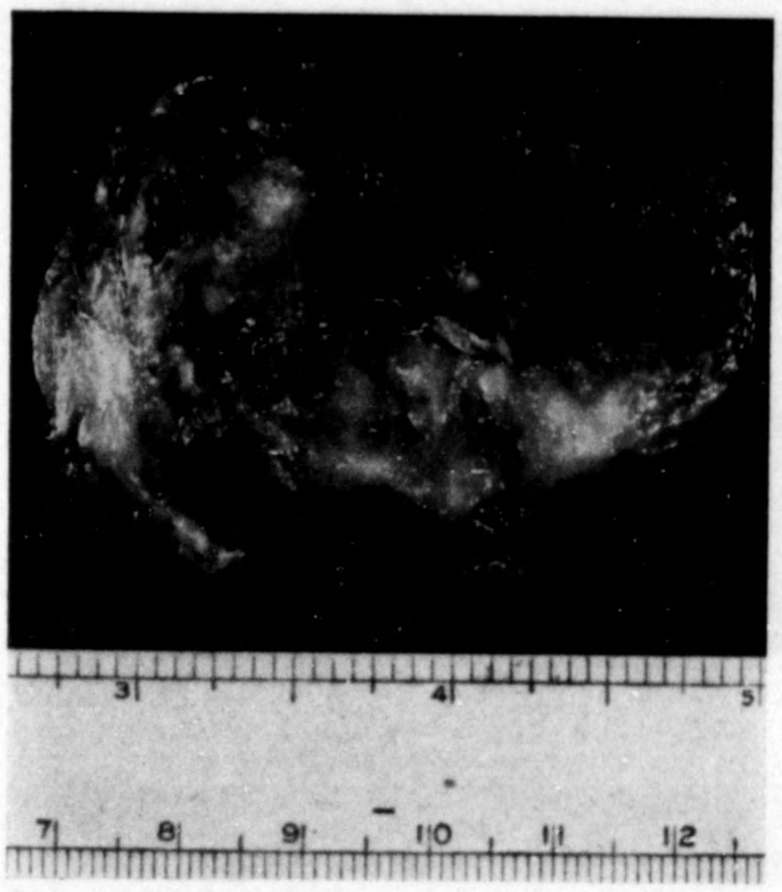

FIG. 2. Case 1. Tumor removed at operation

group. The tissue presented considerable variability in the size and number of the *blood vessels*. In some areas almost an angiomatous appearance was presented; in another only a few scattered small blood vessels were evident. Some small collections of *lymphocytes* were found in the region of some of these vessels. Small irregular *calcospherites* were found scattered throughout the tumor tissue, evidently seated within small occluded blood vessels.

One of the essential cellular elements in the tumor was the *ganglion cell*,—large, irregular, and variously sized elements which were found in clusters about the blood vessels ("cell nests") (fig. 3, *B*), or scattered more diffusely about the stroma. The amount of cytoplasm varied with the size of the cell (fig. 3, *C*). Many had but one nucleus, some had two, and a few had three or even more. The multinucleated cells formed tumor giant cells (fig. 3, *D*). There was also considerable variation in the size and shape of these nuclei, which had the clear vesicular appearance of those normally resident in nerve cells. The nucleolus was likewise typical. Within the

nuclei, inclusion bodies and vacuoles were often found. Direct cell division seemed to be the rule, since no mitotic figures could be discovered.

The cytoplasm of these cells was finely granular in appearance, and the larger, well preserved, usually mononuclear cells showed crescentic condensations of tigroid material at their periphery, a finding emphasized in the cyanin preparations. Many

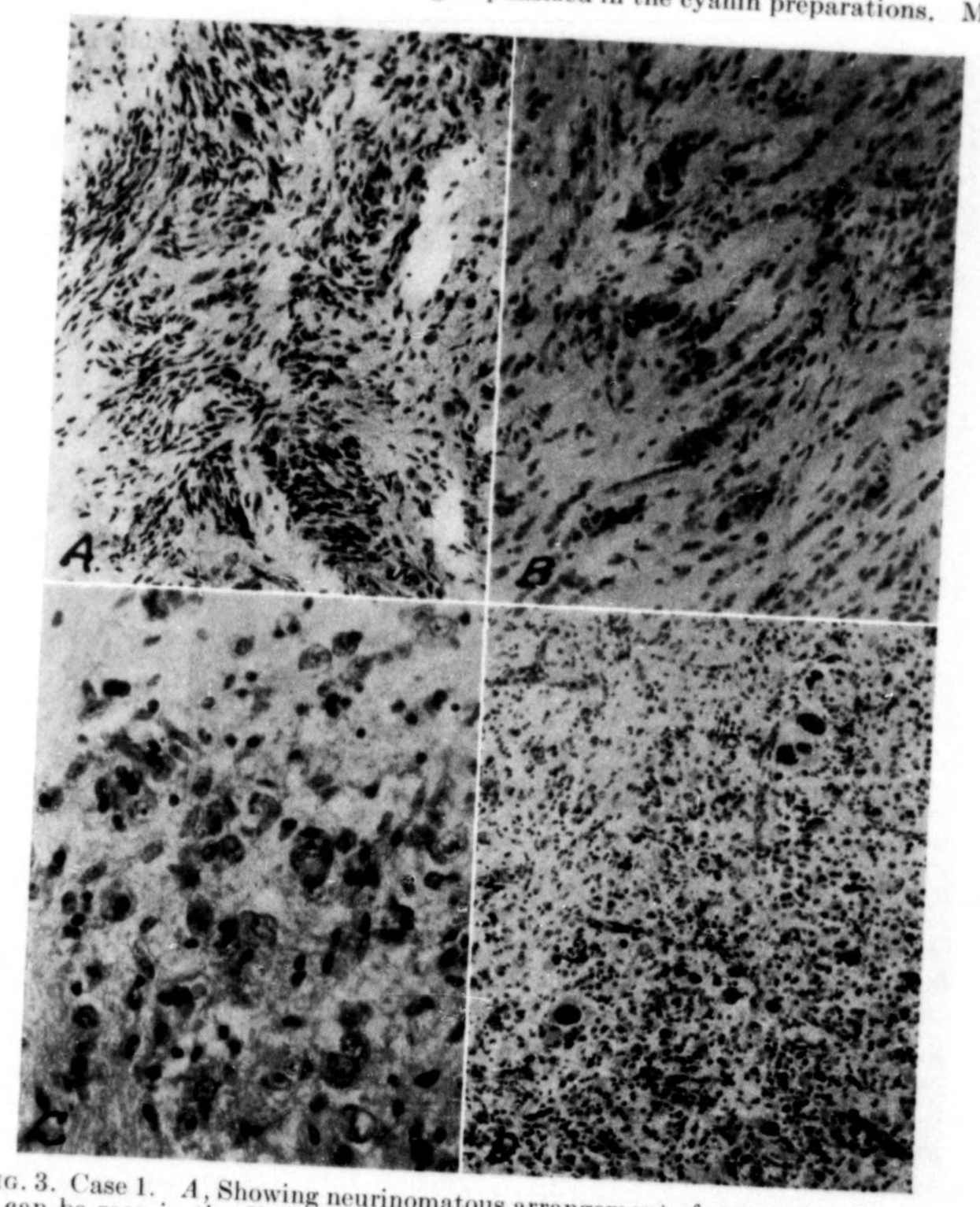

FIG. 3. Case 1. *A*, Showing neurinomatous arrangement of tumor tissue. Nerve cells can be seen in the fibrous areas. H. and E. × 100. *B*, "*Bildungsnester*," or proliferation centers of developing nerve cells. Cyanin stain, × 120. *C*, Ganglion cells. Nuclei of glial elements are also evident. H. and E. × 245. *D*, Giant cells in more actively developing portion of the tumor, H. and E. × 90.

of the larger mononuclear cells were undergoing definite regressive change as indicated by solution of their cell membrane, increased friability of their cytoplasm and disruption of the nuclear membrane. In some of these cells, the granular appearance of the cytoplasm was accentuated. This was emphasized particularly in the reduced silver preparations.

The sections impregnated with silver by the Bielschowsky method clearly indicated that immature as well as mature forms of nerve cells were present in the tumor (fig. 4, *A*). Many apolar, unipolar, and bipolar cells were found. These cells were located in both the reticular and fibrous portions of the tumor. A few of these immature cells were multipolar. While these cells could be found everywhere through-

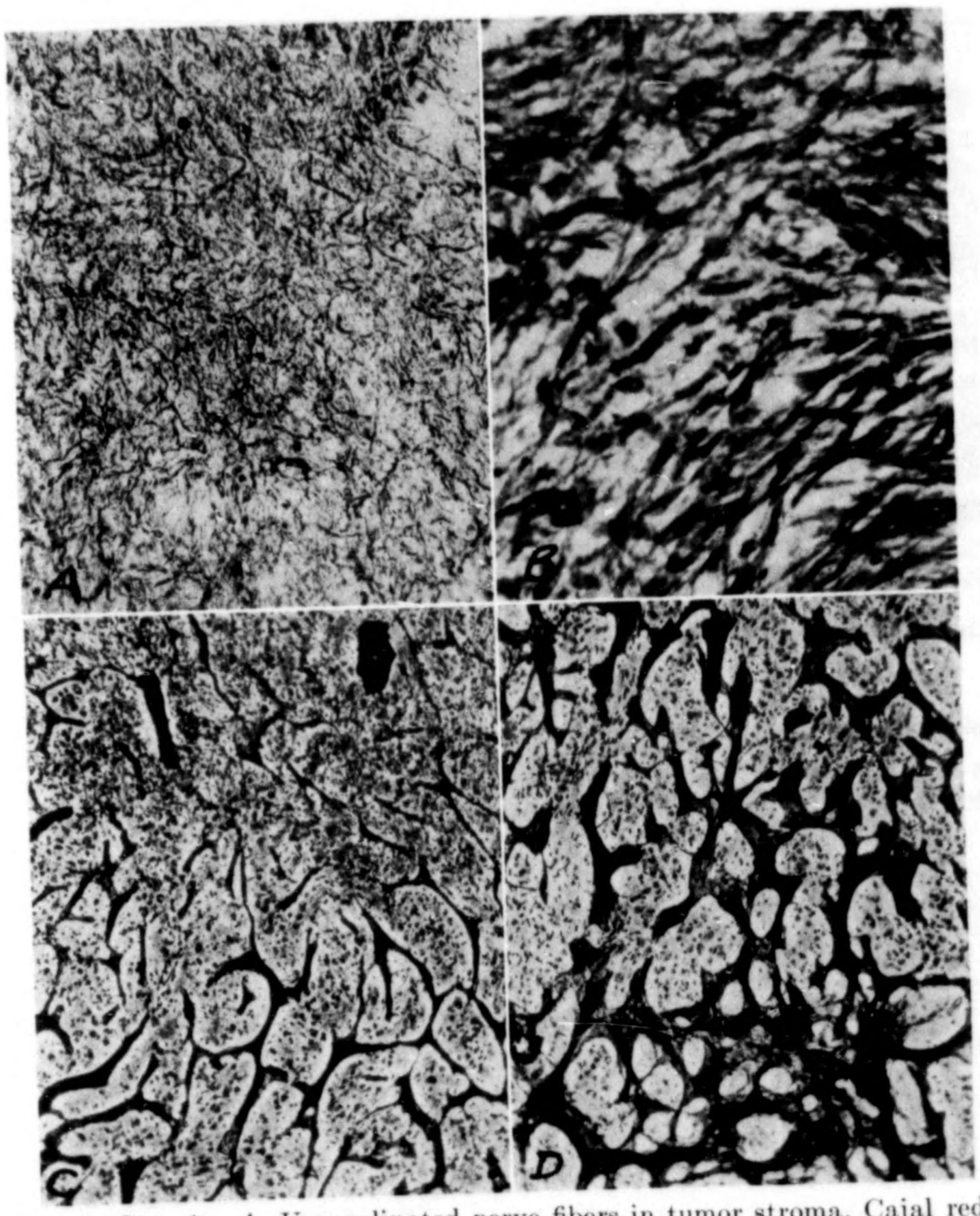

FIG. 4. Case 1. *A*, Unmyelinated nerve fibers in tumor stroma, Cajal reduced silver stain × 190. *B*, Bipolar 'neuroblasts' in fibrous portion of the tumor. Bielschowsky's silver method × 385. *C*, and *D*, Connective tissue stroma in various portions of the tumor. Perdrau's method × 125.

out the tumor, they were most abundant in the "cell nests." Double forms of the bipolar cells indicated direct cell division, one tail of the cell going with each of the two daughter nuclei. The cytoplasm of these immature cells were both granular and fibrillary in this preparation. The nature cells also showed granulation and some fibrillation as well. Many unmyelinated but no myelinated fibers are found in the fibrous portions of the tumor (fig. 4, *B*).

Cellular elements of *glial nature* constituted much of the fibrous portion of the tumor. These elements were unmistakable in their long fusiform cell bodies and oval or elongated nuclei with well developed nuclear membrane and finely divided chromatin content. These cells entered largely into the structure of the neurinomatous portions of the tumor. While these elements were poorly demonstrated by the gold sublimate method, occasional apolar, unipolar, and bipolar forms were found which were well impregnated. A few adult forms, somewhat suggestive of monster glia, probably represented non-neoplastic cells enveloped by the growing tumor.

The *connective tissue stroma* was characteristic. Where this structure was less dense it was found to be limited to the walls of the blood vessels. In adjoining areas it increased in amount until a solid scar was formed (fig. 4, *C* and 4, *D*).

Comment. In this case, a classic type of nerve cell-neuroglia containing tumor was completely removed surgically from the right parietal region, being sharply delineated from the adjacent brain tissue against which it was seated in the wall of a large cyst. As fortune would have it, the patient succumbed in shock about twenty-four hours later.

The structure of the tumor was typical of the group,—the neurinomatous arrangement, the presence of mature and immature ganglion cells and neuroglia, the heavy connective tissue stroma, the perivascular lymphocytic collections, and the calcospherites, all went to make the picture an unmistakable one.

Case 2.* *Progressive failure of vision leading to blindness in the course of three years in a nine-year-old boy. Frontal headaches, projectile vomiting with loss of weight associated with increased drowsiness. Erosion of posterior clinoids and dorsum sellae demonstrated radiographically. Internal hydrocephalus shown on ventriculograms probably due to an obstruction in the third ventricle. Surgical removal of seven grams of tumor from the third ventricle. Characteristic ganglioglioma demonstrated in histologic preparations.*

The patient, a white boy of nine years, was admitted to the Neurological Clinic (Case No. 130–712) of the senior author at the College of Medical Evangelists on October 8, 1939, with the history of progressive impairment of vision since the age of six, loss of appetite and loss of weight for three months, increasing fatigability for two months and nausea and vomiting for one month. The defective vision should have been suspected even before this, since the boy was unusually clumsy and "stumbled over things." But it was not until he started to school that one of his teachers noticed that he could not see as well as he should. It was then observed that he had a peculiar oscillating movement of the eyeballs. His vision failed progressively until at the time of examination he was able to distinguish only the form of objects. At this time he was attending a school for the blind. For three months prior to admission to the Clinic, loss of appetite was followed by nausea and vomiting, at times projectile, increasing fatigability and loss of weight. Frontal headaches, chiefly left sided with occasional occipital localization, had become increasingly severe.

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* The surgical features of this case are being emphasized in an article entitled "Ganglion-cell Tumor—Ganglioglioma—of the Third Ventricle. Operative Removal with Clinical Recovery," which has been submitted for publication by Drs. Adelstein and Anderson.

It was learned that the boy's maternal grandmother had had a 'brain tumor' with symptoms resembling those of the patient.

On examination, the boy proved to be poorly nourished. He was almost completely blind. The eyeballs were in constant motion. The pupils were large and unequal, the right being greater than the left. Optic atrophy was present. The superficial veins in the scalp were engorged, suggesting an increase in intracranial pressure. The boy appeared restless, making irregular, purposeless movements with his hands. No evidence of motor or sensory disturbances were found and the reflexes were thought to be physiological.

The child was referred from the Neurological Clinic to the Neurological Service of the Los Angeles County Hospital on October 30, 1939, for surgical attention with the diagnosis of a third ventricle tumor. Here the boy was found to be mentally

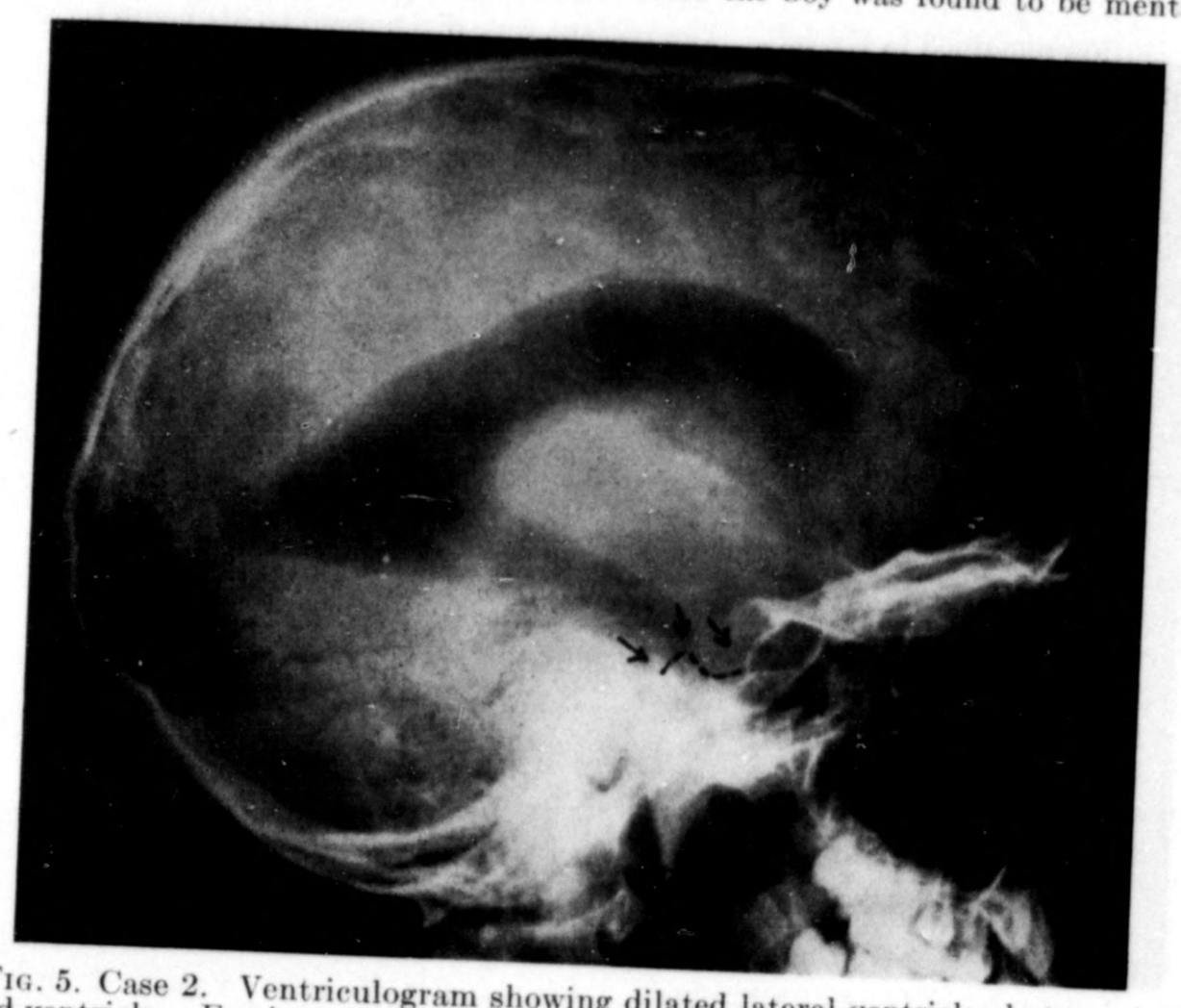

FIG. 5. Case 2. Ventriculogram showing dilated lateral ventricles but no air in third ventricle. Erosion of dorsum sellae is indicated by arrows.

alert, fully oriented and cooperative but with advanced impairment of vision. He was just able to make out fingers at six feet with the left eye but at only one foot with the right. He complained of frontal and occipital headache. There was some tenderness on pressure in the suboccipital region. The percussion note over the skull was high pitched. The left pupil was slightly larger than the right, both were irregular but reacted slightly to light and accommodation. A marked rotatory nystagmus was present on looking in all directions. Both optic disks were pale and their margins were obscured. A left homonymous hemianopia was suspected. No cranial nerve palsies were evident and hearing was not reduced subjectively or objectively.

Radiographs of the skull, taken on November 6, 1939, showed an erosion of the dorsum sellae and posterior clinoids. The convolutional markings also were unduly prominent.

A ventricular puncture and injection of air were done on November 9, 1939, by one of us (Dr. Anderson). The ventriculograms disclosed a marked but symmetrical dilatation of the lateral ventricles but no air was found in the third ventricle (fig. 5). On this basis, a diagnosis of a tumor of the third ventricle was made. The patient was returned to the operating room and a right frontal bone flap was turned down under avertin and local anesthesia by Dr. Adelstein and Dr. Anderson. The third ventricle was entered through the transfrontal route. An encapsulated, firm, pinkish-colored tumor was found in the third ventricle and separated from its bed without excessive bleeding.

The patient was in a somewhat precarious state after the operation. He became increasingly stuporous for some days, finally taking a turn for the better. A residual right hemiparesis was evident. Vision was practically gone in the right eye but light perception remained in the left. The patient was discharged to his home by ambulance on December 7, 1939.

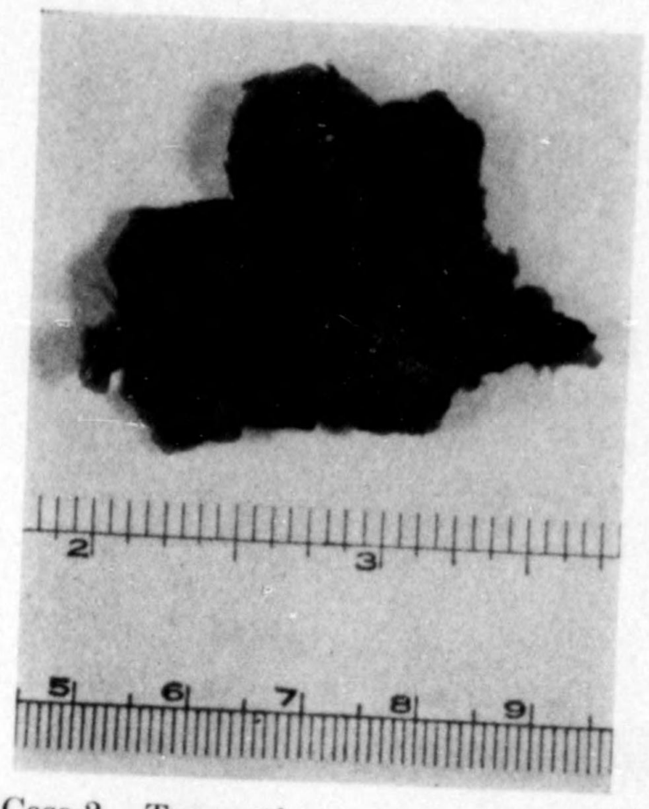

FIG. 6. Case 2. Tumor tissue removed at operation

The patient has been seen recently by one of us (Dr. Anderson). His general health is good but he is totally blind.

The surgical specimen (No. 39-4472) was sent to the Cajal Laboratory for study. It proved to be a group of fragments of tissue of firm consistency the mass of which measured four by three centimeters in its greatest diameters (fig. 6). The tissue weighed seven grams.

The *architecture* of the tumor, while unmistakable in its structure, was not as typical as is often seen in gangliogliomas in this location. The fibrous portion of the tumor consisted of small scattered masses of tissue arranged in loose interwoven strands, ofttimes condensed in the vicinity of blood vessels. Typical pseudopalisading was wanting, only the irregular crisscrossing of the fibers giving a faint resemblance to a neurinomatous structure (fig. 7, *A*). The tumor tissue was rather loose, owing to the relatively large amount of reticular tissue, a situation perhaps exaggerated by the disruption incident to surgical removal. The *blood vessels* were of moderate size, were well formed and not particularly abundant. A few small perivascular collections of *lymphocytes* were observed. No calcospherites were found in the sections studied.

The *ganglion cell elements* were less numerous and less active from a neobiologic standpoint than was the tumor in the case previously described. The cells were scattered throughout the reticular portions of the tumor, no well-defined "cell nests" being discovered (fig. 7, *B*). The majority of these cells had but a single large vesicu-

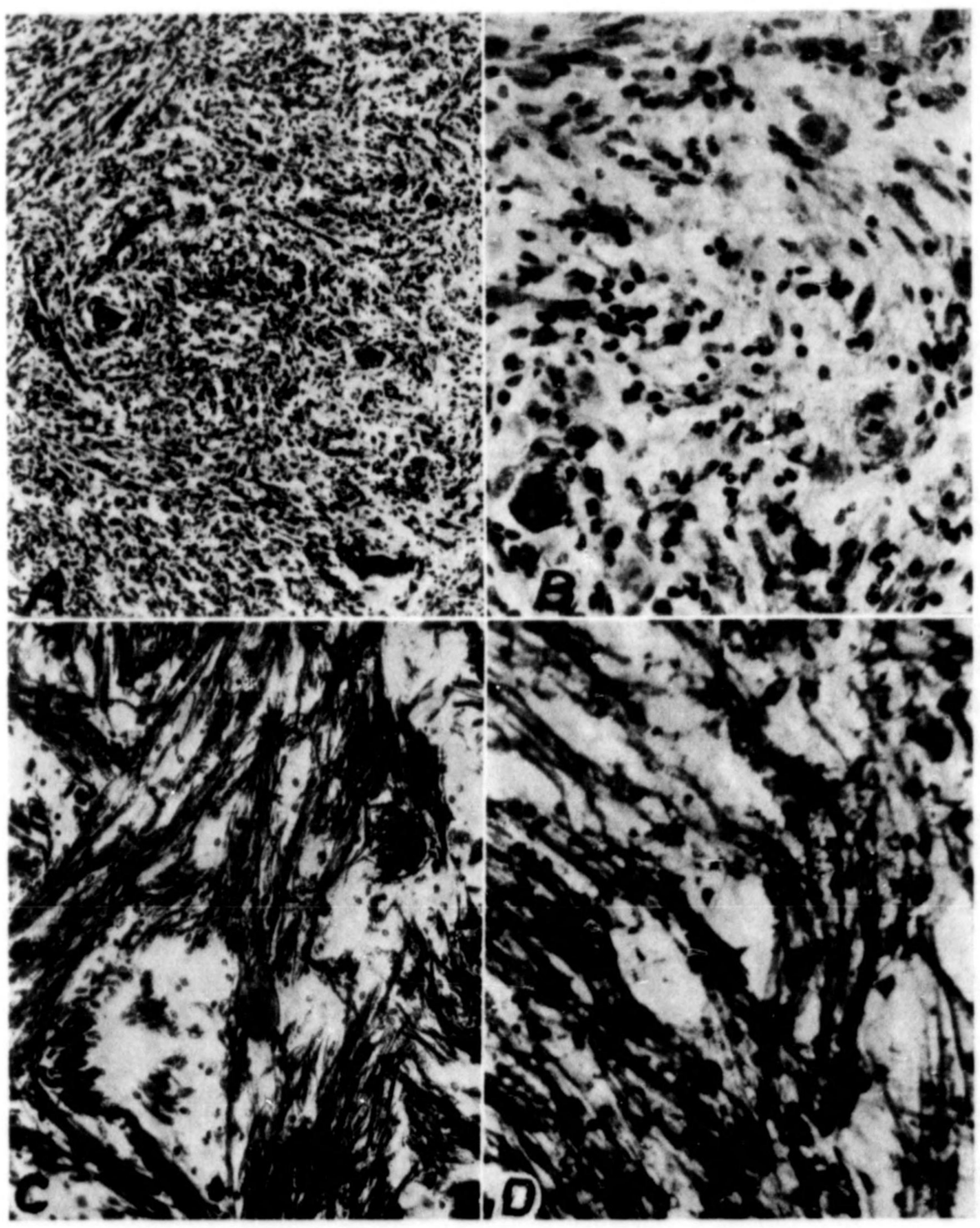

FIG. 7. Case 2. *A*, Showing only feeble attempt at simulation of neurinomatous architecture, H. and E. × 80. *B*, Ganglion cells and nuclei of gliogenic elements in stroma. H. and E. × 245. *C*, Unmyelinated nerve fibers in loose stroma, Cajal reduced silver stain × 150. *D*, Neuroblasts and nerve fibers in stroma. Bielschowsky's silver method × 245.

lar nucleus with a typical nucleolus. This solitary nucleus was often eccentric. Fewer binuclear forms and only rare giant cells were seen.

The cyanin stain disclosed a number of these neuronal elements to be immature forms having no processes, or in some instances one or two polar expansions. The silver method of Bielschowsky showed some fibrillary elements in both the mature

and immature forms (fig. 7, C). The reduced silver method (Cajal) showed the characteristic granular appearance of these larger cells. The silver stain also showed that a considerable portion of the stroma was made up of unmyelinated nerve fibers (fig. 7, *D*).

A goodly proportion of these larger cells were undergoing regressive change as evidenced by disintegration of the cytoplasm and solution of the nuclear membrane. These disintegrating cells were usually mononuclear elements.

The *glial elements* were found in both the fibrous and reticular portions of the tumor and were to be identified by their smaller oval nuclei with well-defined nuclear membrane and finely-divided chromatin contents. Multinucleation was also present in these cells.

The *stroma* of the tumor was moderately well developed but in the sections studied was largely confined to the walls of the blood vessels.

Comment. This case is another of the largest group of nerve cell tumors which have their origin from the floor of the third ventricle, the seventeenth to be reported. The tumor was evidently quite benign, judging not only from the tissue removed at operation but also from the fact that the boy is alive and well two years after surgical removal. While not as classical as the first tumor, the growth was unmistakably a ganglioglioma.

MATTERS OF CURRENT INTEREST PERTAINING TO NEURO-GLIOGENIC TUMORS OF THE BRAIN

While this group of tumors of the central nervous system is a relatively small one, a sufficiently large series of cases has been reported to be able to visualize some of the problems which are not yet entirely solved (Table I). It is our purpose in this connection to consider some of these matters, both in the light of previous studies on this tumor and on the basis of five examples of the growth now available to the writers for their personal study. Put in the form of questions, the important problems of present-day interest may be presented as follows: What is the relative incidence of these tumors among other tumors of the brain? What are the sites of special predilection of their growth? Are there any special gross characteristics which might serve to distinguish them from other tumors of the glioma group? What is the significance of the 'mature' and 'immature' cell forms of both neuronal and neuroglial cells? Is an attempt to subdivide the group on this basis desirable or necessary? How should this group of tumors be designated if classification is not advisable? What is the relationship of this tumor to others of the glioma group, particularly the polar spongioblastoma?

INCIDENCE OF NEURO-GLIOGENIC TUMORS AMONG INTRACRANIAL TUMORS IN GENERAL AND GLIOMAS IN PARTICULAR

The question of the incidence of gangliogliomas is a difficult one to adequately and accurately answer. In the first place those who have reported such cases in any numbers have not taken the trouble to state the number

TABLE I

Reported Cases of Ganglioglioma of the Central Nervous System

NUMBER	AUTHOR	YEAR	AGE	SEX	DURATION OF SYMPTOMS	SIDE	GROSS APPEARANCE
A. Tumors Arising from the Floor of the IIIrd Ventricle							
1	Robertson	1915	42	M	3 yrs.		Mural nodule 2.5 cm. in cyst
2	Greenfield	1918	26	F	3 yrs.		Multinodular, beneath IIIrd ventricle*
3	Josephy	1924	22	F			Infiltrating tumor at base of brain*
4	MacPherson	1925	?	?	?		Calcareous, extending into thalamus
5	Perkins	1926	16	M	3 wks.		Smooth nodule, 3 x 4 x 2.5 cm.
6	Marinesco	1926	40	F	?		Parainfundibular, size pigeon's egg*
7	Horrax and Bailey #2	1928	7	M	4 yrs.		(Biopsy specimen)
8	Courville #1	1930	15	F	15 yrs.		Mural nodule 3 x 2.5 x 1.5 cm. in cyst
9	Courville #2	1930	?	?	?		Minute nodule in tuber cinereum
10	Alpers and Grant	1931	16	M	4 yrs.		(Biopsy specimen)
11	Kernohan et al. #4	1932	13	F	2 yrs.		Extensive, poorly outlined, cystic
12	Kernohan et al. #5	1932	23	M	6 mos.		Hemorrhagic and cystic tumor
13	Foerster et al.	1932	8	F	1 yr.		Cystic nodule 4.5 cm. in size
14	Foerster and Gagel	1933	4	M	4 yrs.		Egg-shaped, cystic tumor
15	Foerster et al.	1933	4	M	3½ yrs.		Tumor size of hen's egg
16	Hoffman and Matulay	1933	23	F	7 mos.		Lobulated granular tumor
17	Courville and Anderson #2	1941	9	M	3 yrs.		(Biopsy specimen)
B. Gangliogliomas of the Temporal Lobe							
1	Schmincke	1910	17	M	9 yrs.	R	Granular tumor size of walnut
2	Katzenstein	1910	16	M	10 yrs.	R	Granular tumor size of walnut
3	Uyeyama #1	1913	61	F	4 wks.	L	Firm tumor with small hemorrhages
4	Schmincke	1914	17	M	?		Granular tumor size of walnut
5	Bielschowsky and Henneberg #1	1928	16	F	11 yrs.	L	Walnut sized tumor with large cyst
6	Bielschowsky and Henneberg #2	1928	11	F	7 yrs.	R	Tumor 2.5 cm. in size with small cyst†
7	Courville	1931	35	F	9 mos.	R	Tumor 2.6 x 2.8 cm. with small cyst
8	Kernohan et al. #1	1932	22	F	6 yrs.	L	(Biopsy specimen)
9	Kernohan et al. #2	1932	39	M	1 yr.	L	Necrotic tumor 4 cm. in diameter
10	Töppich	1936	49	F	16 yrs.	L	Diffuse cortical tumor
11	Wolf and Morton #1	1937	19	F	5 yrs.	L	Tumor 6 x 5 x 2.5 cm., lobulated and cystic
C. Gangliogliomas of the Parieto-occipital Region							
1	Worcester	1901	42	M	5 yrs.	L	Mural nodule 2.5 cm. in large cyst
2	Dumas	1904	29	F	1 yr.	R	Cherry sized tumor near ventricle
3	Uyeyama #2	1913	69	M	?	L	Firm hemorrhagic tumor
4	Olivecrona #1	1919	39	M	1 wk.	R	Firm tumor 6 x 7 cm. in size
5	Wätjen	1930	34	F	6 yrs.	R	Apple-sized necrotic tumor
6	Kernohan et al.	1932	39	F	5 mos.	R	(Biopsy material)
7	Courville and Anderson #1	1941	8	M	6 yrs.	R	Firm walnut-size tumor with cyst
D. Gangliogliomas of the Frontal Lobe							
1	McKennan and Proescher	1908	39	M	3 mos.	R	Sharply outlined subcortical tumor
2	Olivecrona #2	1919	?	F	?	R	Firm reddish-gray tumor
3	Kernohan et al. #3	1932	39	M	6 mos.	L	Extensive tumor with necrosis
4	Kernohan et al. #6	1932	36	F	1½ yrs.	R	Nodule 15 x 18 mm.
5	Cox	1932	49	M	2 mos.	L	Firm cystic granular tumor
6	Wolf and Morton #2	1937	11	M	3 yrs.	L	Nodule in cyst 2 x 1.5 x 0.5 cm.

* These tumors apparently rose from the ventral surface of the floor of the IIIrd ventricle. Two were muitinodular and diffuse, one circumscribed.

† In this case a second tumor was found on the inferior surface of the cerebellum (see cerebellar group).

TABLE I—*Concluded*

NUMBER	AUTHOR	YEAR	AGE	SEX	DURATION OF SYMPTOMS	SIDE	GROSS APPEARANCE
E. Gangliogliomas of the Cerebellum							
1	Achucarro	1913	20	M	2 yrs.	L	Firm gray mass with cyst
2	Lhermitte and Duclos	1920	36	M	1 yr.	L	Diffuse hypertrophy of cortex
3	Paul	1926	6	M	6 wks.	Verm.	Tumor size of walnut
4	Schmidt	1926	45	M	10 yrs.	L	Diffuse hypertrophy of cortex
5	Bielschowsky and Henneberg #2	1928	11	F	7 yrs.	R	Small nodule, ? metastatic‡
6	Bielschowsky and Simon	1930	20	F	2 yrs.	R	Diffuse hypertrophy of cortex
7	Barten	1934	37	F	7 yrs.	R	Diffuse hypertrophy of cortex
F. Gangliogliomas of the Cerebrospinal Neuraxis							
1	Pick and Bielschowsky	1911	24	F	?		Firm elongated tumor medulla and cervical spinal cord
2	Bielschowsky	1925	26	M	15 yrs.		Multiple nodules of pons and ventricles
3	Kernohan et al. #8	1932	34	F	3 yrs.		(Biopsy material) cervical cord
4	Kernohan et al. #9	1932	27	F	4½ yrs.		Cervical cord, 1–8
5	Foerster and Gagel	1932	11	M	3 yrs.		Pons, medulla to 3 cervical
6	Foerster and Gagel	1932	14	M	6 yrs.		Medulla into upper cervical cord
G. Gangliogliomas of Other Locations							
1	Berblinger	1917	17	F	?		Firm nut-sized tumor of left side septum pellucidum
2	Horrax and Bailey #1	1928	40	M	15 mos.		Small circumscribed tumor of pineal
3	Schmincke	1930	50	M	6 mos.		Hazel-nut-sized tumor of pineal

‡ This tumor was suspected of being "metastatic" from tumor in temporal lobe (see temporal lobe group).

of verified tumors of the brain available in that particular clinic at the time the study was made. It would be interesting to know what the relative incidence of this tumor is in the larger clinics from which the reports have issued, such as that of Cushing (Horrax and Bailey reported but two cases), of the Charité in Berlin (Bielschowsky and his associates reported five cases), of the University of Pennsylvania (Alpers and Grant reported but one case), of the Mayo Clinic (nine cases reported) and of Foerster's Clinic in Breslau (five cases reported). It is significant that, when studiously looked for in any large amount of pathologic material a fairly good number of cases seem to present themselves. It is also significant that certain observers who have become familiar with the microscopic characteristics of the lesion have reported several examples (Schmincke, four cases; Bielschowsky and associates, five cases; Kernohan *et al*, nine cases; Foerster *et al*, five cases; and the senior author, five cases). It would follow that, in some clinics at least, the tumor is being incorrectly classified, some of them possibly being grouped with the polar spongioblastomas (see subsequent discussion on this point).

As a possible example of this situation, what seems from the reproduced photomicrograph to be a fairly typical example of a ganglioglioma is

described by Cushing in his monograph on "Intracranial Tumours" (p. 128). The cells forming this tumor show the variability in size and shape so characteristic of gangliogliomas, and what is more, they present a vesicular nucleus and large nucleolus clearly discernible in the illustration. Cushing had this to say about this tumor:

> "One or two of these tumours have similarly been removed from the cerebral hemispheres of children with recovery and have shown no tendency to recur though they were diagnosed at the time of removal as probable sarcomas of the brain. One of them was an enucleable 273-gram tumour, which has been elsewhere described (Am. J. Dis. Children 33:551–584 (Case 1), 1927), was called an ependymoblastoma by the pathologists but we regard it as a fibrosarcoma because of the abundant connective tissue. The child from whose brain this large tumour was removed, now five years later, continues in perfect health. These large, enucleable sarcomas of the brain in children undoubtedly need further study."

In this case we have a benign tumor in a child composed of what seems to be classical immature ganglion cells and an abundant connective tissue stroma so typical of gangliogliomas.

It is also of interest to note two other possible examples of this tumor as reported by Dr. Walter Dandy in his unique study on "Benign Tumors in the Third Ventricle of the Brain." In Case 6 (Group II), a firm, reddish-brown tumor was shelled out of its bed in the third ventricle "with scarcely any bleeding" with complete recovery of the patient, a fifteen-year-old girl. The reproduced photomicrograph (Fig. 61, p. 68) shows large, irregularly shaped cells with vesicular nuclei and large nucleoli which resemble immature ganglion cells. In Case 7 (Group II), a similar but somewhat larger tumor was removed at operation from a twelve-year-old girl. A firm, reddish-brown encapsulated growth was found arising apparently from the septum pellucidium. Like the tumor in the previous case, this one was made up of large, irregularly shaped cells with large vesicular nuclei enclosing evident nucleoli. These cases, if actually examples of the tumor under consideration, indicate what can be done surgically if the tumor is correctly diagnosed and correctly approached. If technical difficulties are not insurmountable, the prognosis should be better than in most other gliomas of the brain.

In the Registry for intracranial tumors in the Cajal Laboratory, there is a total number of 1166 intracranial tumors, of which 581 belong to the glioma group. On this basis the incidence of gangliogliomas in this community as compared with intracranial tumors in general is 0.4 per cent, and with gliomas 0.8 per cent.

SITES OF PREDILECTION

Judging from the cases of this type of tumor now available for study, the most common site seems to be the floor of the third ventricle, seventeen

examples of ganglioglioma in this location now having been reported. The temporal lobe is next in order of frequence, with eleven cases reported. The frontal lobe, the parieto-occipital region, the cerebrospinal neuraxis and the cerebellum appear to be about equally affected. On the basis of these figures, it would seem that, for some peculiar reason, the floor of the third ventricle is most likely to be the point of origin for the tumor. It may also be significant that the average age for the third ventricle group is 18.7 years, while the average for the other groups is 30.1 years. The reason for localization in the floor of the third ventricle can only be conjectured at, the possible complexity of arrangement of nerve cells and neuroglia in the hypothalamus is to be considered. Peculiarly enough, the not-too-far-removed corpus striatum and thalamus have never been found to be the primary seat of one of these tumors.

GROSS APPEARANCES OF THE TUMOR

There are certain features of this new growth which identify it with tumors of the glioma group. There are also a number of characteristics which collectively help to make for it an identity quite its own. These features are its small size, its firm structure, its sharp delineation from the enveloping brain tissue, its association with cysts large and small, and its tendency to contain calcospherites.

As a rule, the tumors have been small in *size*, although there have been some notable exceptions (Olivecrona, Case 2; Watjen; Foerster, McLean and Gagel). The average size seems to be about that of a walnut, a comparison which has been made in so many cases. In one of Bielschowsky's cases (1925), some of the multiple tumors were very small.

As a rule, these tumors are *sharply delineated* from the enveloping nervous tissue, particularly when seen at autopsy. At the operating table some of them have shelled out of their beds easily and with very little bleeding. When definitely identified, this fact should enable the surgeon to 'enucleate' the tumor, it not being necessary to make a wide dissection with loss of functioning nervous tissue and danger of hemorrhage. When observed arising from the floor of the third ventricle they present a smooth surface due to the ependyma which is reflected over its superior aspect. Strictly speaking, gangliogliomas are not encapsulated. In a few cases, the outlines of the tumor have not been evident, particularly when exposed surgically.

In *color*, the tumors are pinkish, reddish-brown, or purplish in color when viewed externally. On cut section, they present a pinkish-gray or darker reddish color, and may present small hemorrhagic foci, although this is more apt to be present in surgical specimens. In texture, especially in fixed tissues, the cut surface of the tumor has a finely granular, 'ground glass' appearance. It is firm in *consistency*, almost rubbery in the fixed

specimen. The tumor may enclose a variable number of small *cyst-like spaces* (cystic glioma) or may be almost wholly enclosed within a large cystic cavity (gliomatous cyst) as is the case with other types of glioma.

One interesting feature which has been described with respect to the temporal lobe group and which indicates its benign character is the *concentric wrinkling of the white matter* at the periphery of the tumor. This has been interpreted as evidence of its slowly expansile growth, as opposed to the more malignant infiltrative gliomas. No other glioma is known to behave in this fashion. As further evidence of its benign character is the occurrence of *calcospherites* located both within the tumor itself and in the compressed white substance at its margin. The presence of these particles may be quite evident on attempt at sectioning or may give a granular feel to the palpating finger. These deposits of calcium are evidently laid down in the walls of the small blood vessels which they ultimately come to occlude.

A special gross form of the tumor which should be mentioned in passing is the diffuse type of ganglioglioma (gangliogliomatosis), involving more particularly the cerebellar cortex and which resembles a hypertrophy of the folia of that organ (Cases of Lhermitte and Duclos, Schmidt, Bielschowsky and Simon, and Barten). This process seems to be a neoplastic transformation of the elements in the cerebellar folia and may represent some profound growth disturbance as the case of Schmidt in particular seems to suggest. Not all cerebellar gangliogliomas are diffuse, however, but may occur in the form of small circumscribed nodules (Paul's case and Case 2 of Bielschowsky and Henneberg) or may be associated with a large cyst (Case of Achúcarro). Nor are all of the diffuse type necessarily confined to the cerebellum. In rate instances, these tumors are not sharply delineated but merge imperceptibly into the normal cerebral cortex and may thus represent a neoplastic transformation of the elements in the cortical gray matter (Case 1 of Olivecrona; possibly some of the cases of Kernohan *et al*).

CELL TYPES IN GANGLIOGLIOMAS

There has been much discussion as to the various types of cells found within these tumors. The invariable presence of mature, though neoplastically atypical ganglion cells was, and still is, chiefly responsible for their primary identification and this observation has caused them to be associated from the outset with the ganglioneuromas of the peripheral nervous system. It was soon learned that immature nerve cells were also present, the occurrence of vesicular nuclei in apolar, unipolar, and bipolar cells making this conclusion an inevitable one. This has also been substantiated by the demonstration of neurofibrillar elements within these immature cells by the silver methods. When these cells are adequately studied

with suitable staining methods capable of demonstrating their cytoplasm, it seems definitely established that immature as well as mature forms will almost invariably be found to be present. In many of the case reports, for want of adequate cytological investigation the presence of immature cells has neither been established nor excluded. At times too much faith has been rested on the results of impregnation methods which are not invariably successful in demonstrating the affinities of these "younger" cells.

Soon after the identity of this tumor was established, the presence of *glial elements* was also discovered. These elements have proven to be truly neoplastic in many if not all of the cases in which special attention was paid to them. In such instances, immature elements seem to be predominant, in fact the adult forms present are considered by some to be incidentally enclosed within the growing tumor and, therefore, play no active part in its neoplastic elaboration.

In most cases it seems clear that the *blood vessels* display no neoplastic activity, although in one of the writers' cases (Case 1) the tumor seemed to be unusually vascular in some areas, more so than is typical of the group.

If the above observations are correct, then *we have to do with a mixed tumor, composed of both mature and immature nerve cells and chiefly immature glial cells.* The variation in the individual tumors seems to depend upon the degree of neoplastic activity of the neuronal elements toward the production of immature forms and the degree of activity of cell division in adult ones, with particular activity in cell division in immature forms of neuroglia. *The more active the neuroglial elements are in this direction, the more closely will the architecture of the tumor resemble the so-called polar spongioblastomas.*

ADVISABILITY OF CLASSIFICATION OF NEURO-GLIOGENIC TUMORS

The variability of the cellular content of these tumors having been recognized, the question of the advisability of subdividing the group comes up for consideration. Kernohan and his collaborators classified their tumors as "neuroblastomas" and "gangliocytomas," depending upon the maturity or immaturity of the ganglion cells. Wolf and Morton have gone much further in this direction and have made four subgroups, i.e., 'ganglioneuroblastoma', 'gangliocytoma', 'gangliogliobla stoma', and 'ganglioglioma'. These terms are more or less self-explanatory, indicating what type cells seem to be present in the tumors.

It must be recognized that at times subdivisions of the larger classes of tumors into subgroups is highly desirable, as has proven to be the case with tumors of the glioma and meningioma groups. But whether it is going to prove profitable to break these subdivisions down once more is open to some question. It seems as though some criteria should be established in this regard. For example, if a given group of tumors tend to

resemble one another in their clinical or neobiologic behavior, or if they show sufficient architectural variation to serve for their ready identification, or if they show typical reactions to radiation therapy, then some practical value exists in attempting such a subclassification.

By applying these criteria to the proposed classification of Wolf and Morton, it seems doubtful whether anything is to be gained by the effort, even though it might possibly be accomplished. If, for example, the group of tumors of the third ventricle is examined, it will be learned that most of them have been designated by these investigators as 'gangliogliogliomas' (? gangliogliomas). This group includes two of the cases previously reported by one of us (Dr. Courville), which tumors, according to this classification, should have been rightly designated as 'gangliogliblastomas' since both mature and immature ganglion cells and glial cells were demonstrated to be present. The remainder of the tumors in this third ventricle group were considered by Wolf and Morton to be 'ganglioneuroblastomas' and 'gangliocytomas'. By this classification in the hands of its proponents, this anatomic group of tumors may contain all of the four varieties. By further study, it is learned that in any given anatomic group, the survival period for any specific type of tumor varies widely. There is, therefore, no close correspondence between the presumed histogenetic nature of the tumor and the survival period. Since we have no evidence that any of the tumors are radiosensitive, we are unable to classify them on this basis.

It seems to the writers that this refined classification, in the light of our present knowledge is undesirable and unnecessary for the following reasons: (1) Such a classification serves no useful clinical purpose. (2) It has no application to any of the anatomic groups of the tumor. (3) It indicates no definite relationship between the apparent neobiologic activity of the tumor and the survival period of the patient. (4) The classification is not based on any structural characteristic which would serve to identify it histologically. It is based instead upon the variables of maturity and immaturity of the constituent cells, a point which would be difficult to establish without careful study by experienced observers. (5) In the hands of its proponents, it seems clear that the reported tumors have not been correctly classified. The tumor in question is essentially benign, it shows no great variation in its architectural make-up, and if the facts were fully known, probably no great variation (other than quantitative) in the types of cellular elements really exists.

It is not for us to say now that this group will never be subdivided, for it is neither our privilege nor power to so restrict the actions of future investigators on this point. But until some one student of the problem has the opportunity to study at first hand a sufficiently large series of cases and to satisfy himself that there is wide enough variation in its structure,

and in its constituent cells and their activity, it seems advisable to leave well enough alone rather than burden the contemporary literature with a nomenclature concerning a tumor, whose total reported cases number less than threescore examples.

NOMENCLATURE

If, then, it seems best not to break down the group of tumors into various subgroups, what collective name should be applied to it? A brief survey of the history of the tumor may be helpful on this point. It became obvious to the pioneer investigators in this field that the term 'ganglioneuroma' which had been applied to its peripheral counterpart was not exact. While both peripheral and central tumors contained ganglion cells, the stroma of central ones contained unmyelinated fibers instead of myelinated ones and, in addition, other elements not of ganglionic character. These 'other elements' proved to be neuroglia cells, mature as well as immature. On this basis the tumor was designated by some as a 'gangliogliomeuroma'. Other terms such as 'neuroglioma' and 'neuroglioma ganglionaire' were also used to indicate the presence of both neurogenic and gliogenic elements.

Some years ago, Ewing proposed the name *ganglioglioma* for this tumor, the term first being used by Perkins in reporting a typical case in which the floor of the third ventricle was the seat of the growth. One of us (Dr. Courville) used this term in previous reports, not because it specifically named all the possible elements within the tumor, but because it was comprehensive in its simplicity. It was, moreover, noncommittal on the problems which have not yet been solved to the satisfaction of all, particularly as to the real significance of the morphological variants in the cells forming the tumors of the glioma group. The objection to the terms 'neuroblastoma' and 'gangliocytomas' is that they specifically identify only one element of a mixed tumor. Moreover, any attempt to name *all* the elements on the assumption of their morphologic resemblance to embryonic forms would only result in hopeless confusion. Even the term 'gangliogliomeblastoma' is not all inclusive and furthermore leaves the impression that the tumor is malignant which it certainly is not, at least in the great majority of cases.

It, therefore, seems to the writers that the term *ganglioglioma* still has much to commend it. It is comprehensive, noncommittal on controversial issues, and simple enough to be used by general pathologists as well as by those concerned with neuropathology alone.

RELATIONSHIP OF GANGLIOGLIOMAS TO POLAR SPONGIOBLASTOMAS

In reporting his case of ganglion cell tumor of the floor of the third ventricle, Josephy commented on its structural resemblance to the peripheral neurinomas, since both of them were made up in part of interlacing

bundles of fibrous elements. It was, therefore, described as a "neurinoma centrale." His tumor has been accepted as a definite case of ganglioglioma by most students of the problem. This seems proven by the fact that the preparations in this case were personally reviewed by Dr. Bernard J. Alpers who pronounced it an unquestioned case of nerve cell tumor. Bailey and Eisenhardt have since classified it, presumably on the basis of its structural appearance, with the polar spongioblastomas. On this basis, this case and a similar one reported by MacPherson have been deleted from the series of ganglion cell tumors by Wolf and Morton, because polar spongioblastomas "commonly occur in this region." This conclusion should not necessarily settle the question for it is also the most common location for gangliogliomas. Moreover, our experience in the Cajal Laboratory does not bear out the idea that such tumors are *commonly* found here, for in a series of 1166 verified intracranial tumors and of 44 tumors of the third ventricle, only one example of polar spongioblastoma has been found in this location. Since the tumors of Josephy and of MacPherson contained ganglion cells, evidently neoplastic, we believe they should be retained in the series.

For a more direct approach to the problem, an investigation of the structure of gangliogliomas is in order. As exemplified by both examples of this tumor herein reported, their fibrous portions were definitely reminiscent of the structure of the peripheral neurinomas, and, therefore, of the polar spongioblastomas. A critical study of these fibrous elements showed them to be largely of glial origin. Nevertheless, even in these portions of the tumor, silver preparations demonstrated the unmistakable occurrence of immature ganglion cells ('neuroblasts').

In his previous communications, the senior author of this contribution suggested that some relationship, at least structurally, exists between the gangliogliomas and the polar spongioblastomas. He went so far as to suggest that some of these 'spongioblastomas' arising from the floor of the third ventricle might prove to be gangliogliomas, if a careful search for neoplastic ganglion cells were made. Certain it is that *gangliogliomas in this, and other, locations, contain masses of glial tissue whose architecture is indistinguishable from the polar spongioblastomas.* The greater the amount of glial tissue, the more closely the resemblance will be. No one can say that this resemblance to a peripheral neurinoma establishes the purely glial origin of the tumor while the presence of neoplastic ganglion cells should make its identity certain.

SUMMARY AND CONCLUSIONS

1. This study is concerned with a resurvey of the reported cases of neurogliogenic tumors (gangliogliomas) of the brain, with a report of two additional cases, and a consideration of some of its problems as suggested by various investigators.

2. These tumors are most commonly found arising from the floor of the third ventricle and from the centrum of the temporal lobe. The other parts of the cerebrum, cerebellum, and cerebrospinal neuraxis are about equally affected. Oddly enough, the gray matter of the corpus striatum and the thalamus does not serve as the starting point of this tumor.

3. Grossly, the tumors are usually small, firm, granular, pinkish-gray or reddish colored tumors which are sharply delineated from the enveloping white matter. A few of them arise by diffuse neoplastic transformation of the cerebellar and possibly the cerebral cortex as well. At times the tumor occurs as a mural nodule in the wall of a large cyst, at others it may contain several small cysts. The tumor is rarely multiple and rarely spreads by way of the cerebrospinal fluid passageways.

4. Structurally, the tumor is made up of two types of tissues, a reticular tissue in which atypical nerve cells are found and a fibrous tissue made up largely of glial elements, nerve fibers, and connective tissue. There is a fairly abundant connective tissue stroma in many cases, evidently having its origin from the walls of the blood vessels. Localized perivascular lymphocytic infiltrations and small calcospherites are often found throughout the substance of the tumor.

5. The essential neoplastic cells are both of ganglionic and neuroglial origin. Both mature and immature elements of both cell types are usually present although they cannot always be well demonstrated by impregnation methods. Cytoplasmic stains (such as phosphotungstic acid-hematoxylin or aniline blue), which demonstrate both the morphology (thus indicating its maturity or immaturity), as well as the nuclear structure (which shows the essential ganglionic or glial character) of the cell, are most useful in this regard.

6. Because all tumors of the group show a structural similarity and because no special advantage is gained from attempts at creating subclasses either from a diagnostic or therapeutic standpoint, it still seems advisable for the present to include all examples under one comprehensive term. The designation *ganglioglioma* is sufficiently comprehensive and noncommittal as to avoid controversial issues.

7. The neuroglial portions of the tumor are similar in the structure to the polar spongioblastomas and it is quite likely that the two tumors have often been confused. The presence of neoplastic ganglion cells in the reticular portions of the tumor should serve to identify it definitely as a ganglioglioma.

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A CONTRIBUTION TO THE STUDY OF SINUS PERICRANII (STROMEYER)*

REPORT OF CASE WITH SOME COMMENTS ON PATHOLOGY OF THE LESION

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In spite of the fact that the occurrence of a small, circumscribed and reducible blood-vessel tumor of the scalp and pericranium has been recognized now for almost exactly one hundred years, remarkably few cases have been reported in the English and American literature. Moreover, the exact character of the lesion, its relationship to the larger and much more impressive cirsoid aneurysm of the scalp, and its surgical treatment do not seem to be fully appreciated. Since reports of such lesions are still so rare, it seems worth while to put on record a case which has come to the attention of the present writers. With this report as a point of departure, a survey of the literature has been made with the particular object in mind of studying the pathogenesis and the pathology of the lesion. This is done in an effort to establish the place of this lesion in the larger group of blood-vessel tumors of the scalp and skull and to point out such facts in its structure of pertinence to those who may essay to cure it.

The term "sinus pericranii" has become the one commonly used to designate the lesion in question, a fact in itself interesting, since it was this term by which Stromeyer introduced it to medical science almost a century ago. However, in the early years of its recognition there were many terms by which it was indicated. By the time Mastin wrote his scholarly review, the first important one in the English language, a bevy of names had been used. Among these terms were the following: varix verus circumscriptus; fistula osteo-vasculaire; erectile tumors of the skull; varix sinus verus extracranium congenitalis; varix simplex communicans; venous tumor of the cranial bone; varix spurius circumscriptus venae diploecae frontalis (or elsewhere); sanguinous hernias of the cranial vault; varicose veins of the skull; venous varicosities of the skull; subpericranial venous tumors; reducible sanguinous tumors of the cranial vault; aneurysmal tumors of the temporal (or any other) region; cephalomatocele; hemangioma or cavernoma of the scalp.

The tumefaction which has been subject of such an impressive list of designations has long been recognized as composed of one or more localized congenitally enlarged venous channels lying beneath the scalp and located within the pericranium. These veins have a definite connection with the intracranial venous system by one or more communications through the skull. The "tumor" appears as a soft, fluctuant, low-grade swelling of some portion of the scalp which becomes distended when the head is held in a dependent position, when physical exercise is indulged in, or when, by any other means, the intracranial pressure is raised. The swelling thus formed is readily reduced by compression.

While it may be assumed that these swellings must be much more common

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than the number of reported cases would seem to indicate, remarkably few instances have been recorded. Their history, nevertheless, is an interesting one.

HISTORY OF REDUCIBLE BLOOD TUMORS OF THE SCALP

In the year 1772, in an inaugural dissertation dealing with the dura mater, there was described a small cyst in the occipital region which proved to be filled with coagulated blood and which was found at autopsy to be connected with the superior longitudinal sinus by a fistulous tract. If this lesion described by Beikert[1] is correctly interpreted at this late date, it would appear that this was perhaps the first reported case of sinus pericranii, one of the subtype which has come to be known as an ectasia of the superior longitudinal sinus, or, more technically, a varix herniosus sinus sagittalis. This report appeared some 75 years before that of Stromeyer which came to identify the lesion as a definite entity. Even though this case proved to be one of the rarest types of sinus pericranii, it serves as a point of departure in this brief survey of the history of this unusual lesion. It was not until about four decades later that Pelletau[2] described the first classic case of sinus pericranii, the lesion occurring in the upper frontal region in a 15-year-old male. This was also the first case of the classic type to be verified by autopsy.

In 1831 Berard described a case which seems to be typical of the condition, but this did not come to light until cited by Chassaignac[3] in 1848, who also reported a case of varicose lesion of the scalp of an infant which communicated with the superior longitudinal sinus. Meanwhile Melchiori[4] (1843) had recorded for posterity another case of typical varix racemosus communicans occurring in the left parietal region in a 14-year-old girl, which lesion was also verified at autopsy. Hecker[5] (1845) described a case of a right frontal lesion in a man of 34 years, the first presumed to be of traumatic origin, attributed to falls as an infant in trying to learn to walk.

But even before these cases were recorded, there is the story of a French infantryman who in 1799 sustained a blow in the right frontal region by the butt of a musket wielded by an enemy soldier in the course of a charge on a redoubt. The victim was rendered *hors du combat* and had to be carried from the field in an unconscious condition. When given first aid by an army surgeon a deep depression in the skull was found, and it was assumed that an extensive fracture of that region existed. The soldier lived to tell the tale, and when (in 1847) he was 77 years of age he came under the care of another military surgeon by the name of Hutin, who found a small soft swelling about the size of a nut at the site of injury. This swelling increased in size when the patient inclined his head and then assumed a livid color. It was learned that this swelling had been present since shortly after the original injury and had existed for almost 50 years. The patient died of erysipelas. A postmortem examination of the lesion disclosed distended local veins which communicated with the superior longitudinal sinus through several small openings in the underlying bone.[6] Though presumed to be on a traumatic basis, the lesion seems to be a typical

sinus pericranii. Hutin[7] later reported the case of a French soldier who had received two sabre cuts of the head at the battle of Jena in 1806, wounds which required 9 months to heal. Some 40 years later, while intoxicated, the old soldier fell into a pile of rocks, fracturing one of his femurs. In the delirium which ensued as the result of erysipelas, the patient kept putting his hand to the top of his head, where a local fluctuant swelling was found. When incised, this tumor proved to be a "blood cyst" located between the skull and the pericranium. At autopsy there was found an underlying defect in the bone, evidently the residual lesion of the sabre cuts. This is evidently a second, traumatic type of sinus pericranii. While these two experiences of Hutin were prior to 1850, they were recorded some time thereafter.

It was in 1850 that Stromeyer[8] reported two cases of this lesion which he first designated as sinus "pericranii". One of his cases, occurring in a boy of 6, was evidently a traumatic lesion, apppearing after a fall on the vertex which resulted in a local depressed fracture. The second case was a congenital lesion which occurred in a man of 20 years. The swelling appeared to the left of the midline of the forehead, extending between the superciliary ridge and the hair line. It was the report of these cases by Stromeyer which seemed to stimulate other observers to record their observations, and it is also to him that thanks are due for the introduction of the term which has persisted to the present.

After Stromeyer's report was published, there were a number of cases reported in the next two decades, those of Middeldorf, Verneuil, Foncteau, Demme, Ogle Bruns, Andrews, Larrey, Nelaton and Richard, and Giraldes. By the time Wislicenus[9] presented his two cases in 1869 he was able to collect a series of 26 cases which had appeared in the literature up to that time. A few additional cases are recorded between the thesis of Wislicenus and the monograph of Mastin's[10] published in 1886 (Duplay, 1877; Schellman), but by this time the latter author was able to gather a series of at least 28 cases which seem to be *bona fide* (in addition to several others which seem to be ordinary hematomas of the scalp, chiefly following birth), and to add one which had come under his own observation, a swelling in the left posterior scalp in a man of 35 which became enlarged on stooping over or even after a full meal.

When Cohn wrote his review of the subject in 1926, he was able to refer to a number of other cases which had appeared since Mastin's paper. He referred to the report of Lannelongue[11] which appeared in 1886 in which he reported one of his own cases and reviewed 12 others which he had collected which were assumed to be true congenital (as opposed to traumatic) cases. In the interim Cohn[12] was able to cite 8 additional cases, those of Franke (1902), Arnheim (1908), Hirsch (1910), Krause (1911), Weiting (1911), Mueller (1912), Borchard, (1916) and Moerig (2 cases, 1917). And Cushing[13] had called attention to his two "traumatic" cases in which the lesion made its appearance with the development of an increased intracranial pressure; the exact place occupied by the vascular enlargement in these cases is still debatable.

The last effort to study the problem, at least as far as reports in the English language are concerned, was that of Hahn[14] in 1928, when a case of a typical

lesion was reported in which careful attention was given to the histologic character of the lesion with respect to its intimate characteristics. This report was concerned also with a denial of the importance of trauma as an etiologic factor.

CLINICAL MANIFESTATIONS OF SINUS PERICRANII

The lesion here under consideration presents itself as a circumscribed, soft, fluctuant, compressible swelling of the soft tissues of the scalp. This swelling is said to be most common in the frontal or temporal regions, occurs next most commonly at the vertex to one side or the other of the midline and less often in the parietal or occipital regions, a conclusion which is borne out by a review of the reported cases as a group. This tumor, in many of the reported instances, presents no variation in color from that of the regional skin. In other cases, however, it has been described as livid or violet (Dufour) or violaceous, or more commonly as bluish and bluish red.

The swelling varies in size within certain limits. Perhaps the largest lesions to be described are those of Melchiori and Hecker. Those whose measurements are known are described by Moerig, whose lesion measured 13 x 3.5 cm., and by Wislicenus, whose lesion measured 6.5 x 5 x 2 cm. Usually, however, it is smaller than this and has been repeatedly described as the size of "half the size of a hen's egg" (Bruns), of a pigeon's egg (Hutin), large chestnut (Duplay), of a walnut (Mueller, Moerig), half a walnut (Cushing), hazelnut (Verneuil), acorn (Mastin), large nut (Azam), small plum, 5-franc piece (Larrey), etc. The use of terms suggesting a fair uniformity of size clearly indicates that this limitation in size is an essential characteristic, one which serves to distinguish it from the larger lesion commonly known as cirsoid aneurysm.

As suggested by some of the figures used as well as specific descriptions, some of the lesions are definitely elongated (Moerig's second case), although most of them are irregularly round or oval in shape. Some appear to be almost square, others like a focal rounded eminence (especially the varix herniosus). The surface of the swelling when fully distended may be irregular in contour, and this irregularity in itself may suggest that the underlying vessel is varicose in its contour.

Occasionally some enlargement of the regional superficial veins is apparent (cases of Hirsch, Cushing), but this seems to be quite exceptional and would thus serve to distinguish it from a cirsoid aneurysm of the scalp. The same may be said for pulsation of the lesion which is almost always absent.*

* Pulsations have been described, however, in a few cases. It was found in the second case described by Wislicenus, but here the pulsation was considered to arise from the underlying brain, being communicated to the lesion through a defect in the skull. This was also true in the case of Hirsch, where the pulsations were synchronous with the heart beat and apparent over a fissure. When present, pulsations are usually perceived only when the constituent vessels are fully engorged (Franke, Arnheim), and when evident they are usually very faint and appreciable over the center of the swelling (Duplay). These facts seem to indicate that the pulsations are quite infrequent, faint, and due to transmission of pulsations from the brain rather than to any arterial constituent of the swelling.

Among the other features of the lesion evident on clinical examination is that which indicates some change in the underlying bone. This defect may consist of a small shallow depression (Franke), a depression with an irregular border (Giraldes), a fissure or groove in the skull (Krause), a defect of irregular conformity as with transverse ridges (Wislicenus), or one with a cribriform aspect having multiple palpable openings (Mueller). In some instances the margin may be sharp in some portion of its extent. At times small projections suggesting proliferation of bone may be felt (writer's case), which may provoke some discomfort because of their sharp contour.

Subjective discomforts, usually of minor degree, have sometimes been described as occurring when the lesion is full or when undue pressure is put upon it. Perhaps the most common of these complaints is that of a feeling of fullness and even of weight in the region of the swelling. At times headaches (Hecker) either of a fleeting character (Mastin) or more rarely of sharp and radiating character (Mueller) may occur. These sharper pains may radiate into other parts of the head or down into the neck, suggestively along the course of the intracranial venous channel, with which communication is made. A sense or dizziness or "swimming in the head" (Stromeyer), or a well-marked vertigo has been described in some cases (Hecker, Weiting, Moerig). Vomiting and blurring of vision were mentioned in the recitation of symptoms in Moerig's second case. In the great majority of cases, nevertheless, subjective complaints are so minor as to be overlooked or absent altogether.

Attention having already been called to the fact that the lesion is most apparent during life when in a distended state, it is pertinent to call attention to the means by which this distention occurs. Among the various causes of distention, the following are mentioned by many of the contributors to the subject: assuming a recumbent position or forward inclination of the head, crying, coughing, straining or sneezing, heavy physical exertion, deep breathing, emotional stress, or compression of one or both jugulars. In one of Verneuil's cases, the swelling was more pronounced during the menstrual period. The swelling can be reduced in size by elevation of the head, deep pressure over one or both carotids, compression of the tumor itself, or by taking several deep inspirations. All this goes to prove that turgescence of the lesion is a direct consequence of an increase in intracranial pressure and incidentally of interference with the outflow of venous blood from the head.

In the light of these accumulated observations by numerous observers over the years, the following case which came under the direct observation of one of the present writers for several years may now be profitably presented.

REPORT OF CASE

First appearance of bluish swelling in the left temporal region in a boy of 7 years. Subjective consciousness of the swelling under certain circumstances by the patient at the age of 13. Examination at the age of 16 disclosed swelling in this region which was accentuated by dependent posture and compression of the jugular veins. Re-examination of the patient at 26 with further demonstration of the character of the vascular lesion by the injection of thorotrast. No further change in lesion after seven more years.

(Department of Nervous Diseases, Case No. 816.) A white man, news photographer by vocation, was referred for study by Dr. Leonard Brunie of Pasadena on June 19, 1939. The patient's two complaints were a left internal squint which had been present since he was about 5 years of age, and a swelling in the left temporal region which had been recognized since he was 7 or 8 years of age. The cause of the internal squint was not known, but it had been noticed by his parents when he was about 5 and had persisted ever since. Likewise, the left temporal swelling had remained unchanged since first observed by his parents when he was about 8 years old until he was 13, when he first became subjectively conscious of its presence. It had presented a bluish coloration from the outset, this color being particularly conspicuous when he was cold.

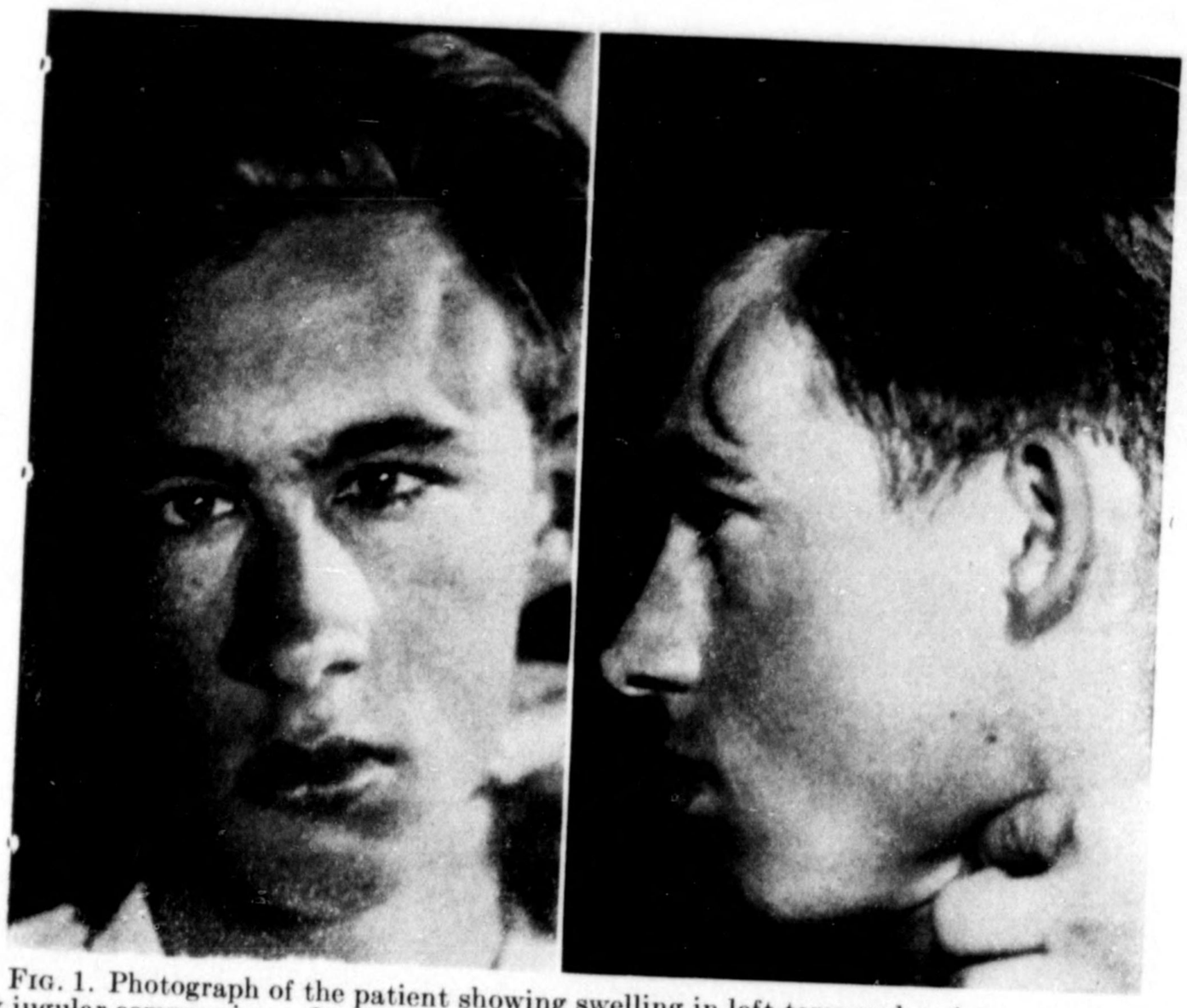

FIG. 1. Photograph of the patient showing swelling in left temporal region, accentuated by jugular compression. Its sharp limitations indicate its pericranial attachments. Congenital left internal squint is also apparent.

The patient had noticed that the swelling became distended on exercise or when his head was held in a dependent position. Under these circumstances the swelling gradually increased in size. At rest or when he assumed an upright position the swelling gradually receded. Steady pressure with the fingers could also empty the sac, although even this measure took some time.

The patient had been seen by the senior author almost a decade before, when he presented himself at the outpatient clinic of the Los Angeles County Hospital (on Apr. 4, 1930) at the age of 16. At this time the lesion appeared as a soft fluctuant tumor mass with a faint bluish coloration in the left temporal region. This tumor mass could be distended by pressure over the jugular veins (fig. 1). Radiographs of the skull showed minor defects in the skull beneath the swelling. Similar films taken about one year after admission (Apr. 17,

1931) disclosed an irregular circumscribed rarefaction which resembled a large diploic space over which a circumscribed, roughly circular shadow could be seen. This was presumed to be a vascular communication between some intracranial venous channel and those of the extracranial tissues. The extracranial shadow was considered to be a large venous sinus. It was evident that there had been some erosion of bone in the region in the intervening year.

When seen again on Feb. 4, 1934, the swelling appeared slightly larger than at the time of previous examination. Radiographs of the skull again showed the extracranial mass, which was now found to be some 6 cm. in diameter in the left fronto-temporal region. Externally the swelling actually measured 6 x 8 cm. It was considered to be a typical sinus pericranii.

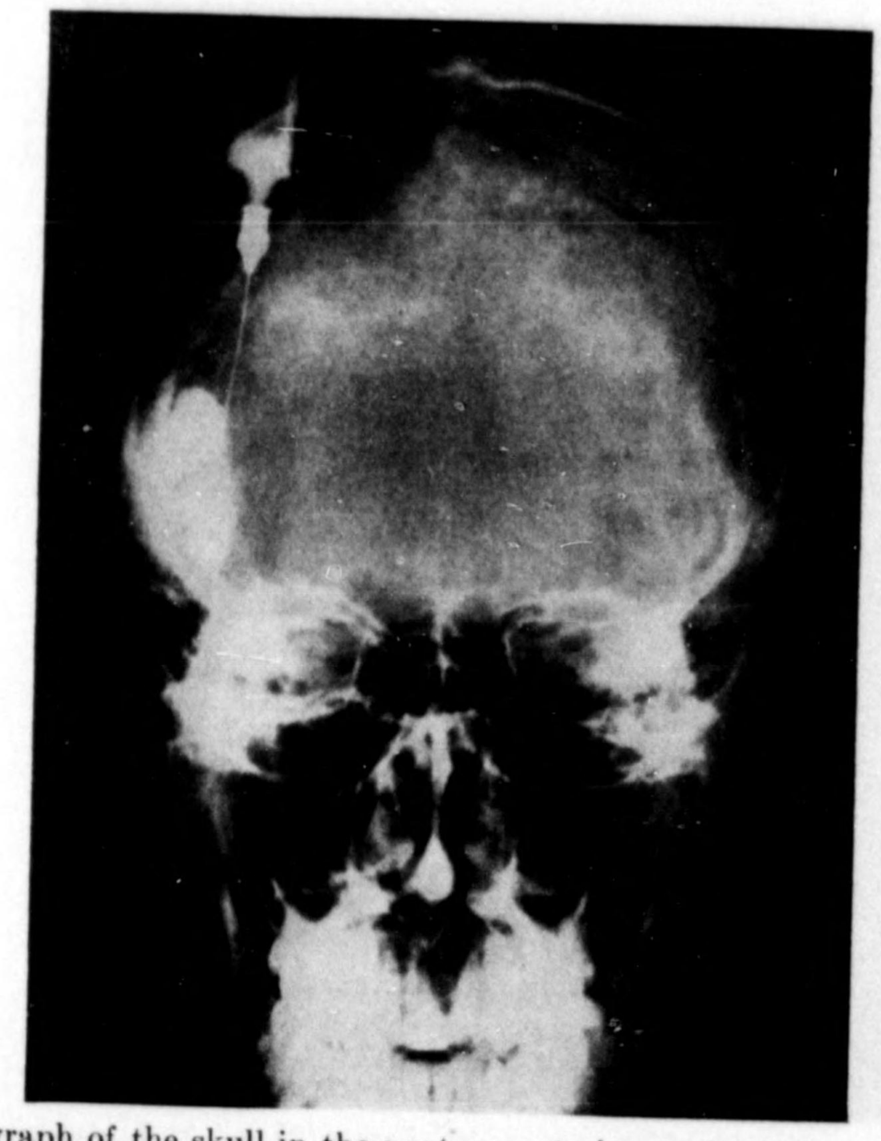

FIG. 2. Radiograph of the skull in the postero-anterior position showing location and character of the lesion after injection with thorotrast.

At the time of the visit on June 19, 1939 the patient stated that the swelling seemed slightly larger than when last seen some 5 years before and that it had become slightly tender on palpation. He thought that he could detect some sharp spike-like projections from the bone at the margin of the swelling. When the swelling was engorged he was conscious of a feeling of pressure and weight. He also mentioned that his hair over the swelling had been very unruly and difficult to keep in place.

The following note was then made of the lesion: "There is a bluish pigmented area in the left temporo-frontal region measuring 4 x 6 cm. in its longest (oblique) diameter. This area swells when the patient lowers his head, and at such a time it is fluctuant and soft, obviously filled with fluid, probably venous blood. When empty the bone beneath can be palpated and presents an irregular surface, as though the outer table had been eroded. A small, spike-like eminence is found on the anterior margin of this swelling. There is also a large flatter mass in the posterior margin of the swelling. These are slightly tender on pressure and may be phleboliths. There is no bruit over the mass or in the vicinity of it.

The eyes are essentially negative, except for a slight internal squint which is still evident in spite of a previous operation for its correction. The left pupil is slightly larger than the right. . . . The optic disk was slightly more pink than was the right, but no venous malformations of any sort were noted in the eyegrounds."

In an effort to demonstrate the extracranial and intracranial venous connections of the sinus, it was proposed that the sac be injected on the x-ray table with thorotrast. If these connections were not excessive, the possibility was considered of injection of hypertonic glucose into the sac with the idea of sclerosing the constituent vessels. This was agreed to, and an injection of thorotrast was made and radiographs of the skull taken immediately thereafter. The venous channels composing the lesions were well demonstrated (fig. 2), but the connections with the intracranial venous channels were not shown. It is now presumed that the sac emptied much slower than was originally presumed and that the small amount of thorotrast which escaped into these communicating channels made no shadow on the film. At any rate, since the vascular lesion could not be definitely isolated, it was deemed unwise to attempt to sclerose the venous channels composing the lesion.

FIG. 3. Radiograph of the skull in the left oblique position showing size of the lesion as demonstrated after injection of thorotrast.

Contact with the patient through a member of his family on Oct. 1, 1946, discloses the fact that the lesion has been essentially unchanged since he was last seen. In the meantime, he has spent 3 years and 8 months in the Navy in the Western Pacific.

Comment. The case here described is one of sinus pericranii which is classic in all its features. The swelling was found to enlarge on any condition in which the intracranial pressure was increased. It was therefore evident that there existed some connection between the extracranial lesion and the intracranial circulation.

That this connection is small is suggested by the fact that the swelling accentuates slowly and is reduced slowly by manual compression. In the 25 years of its history the lesion increased slightly in size during the first few years but has remained quiescent for some time. No disturbing subjective signs have made their appearance.

CLASSIFICATION OF SINUS PERICRANII

Since 1850 when this lesion was officially introduced,[8] it has been recognized that the underlying vascular anomaly was not the same in all cases. Demme (1862) was perhaps the first to attempt to classify the lesion, recognizing the congenital and the traumatic varieties. Mastin[10] (1886) described two anatomic types, (1) the cystic form which consisted essentially of an emissary vein, or ecstasia, originating in the superior longitudinal sinus, and (2) the varicose form, which was characteristic of the great majority of the cases, consisting of a variable number of congenitally enlarged blood vessels. On these two bases, i.e., the etiologic and the anatomic, all other subsequent classifications have been constructed. We find that the etiologic classification has been perhaps the most popular if not the most critical and was used as late as 1928 by Hahn[11], who nevertheless continued to discredit the traumatic type. However, one cannot study some of the earlier reported cases such as those of Dufour (Hutin), Azam and others in which a definite fracture of the skull was the apparent immediate cause of the lesion and in which there arose in the defect of the skull a definite reducible blood tumor without concluding that there is a true traumatic type, rare though it may be. Perhaps Lannelongue[11] went too far even in 1886 to say that the great majority of the lesions were traumatic simply because they were assumed to be so by their reporters. It seems that at most some of the traumatic cases were simply provoked to develop by local injuries, there being a latent venous deformity present prior to the injury. This seems to be the only solid conclusion to be reached, because in some of the alleged traumatic cases there was no clear-cut history of injury in the first place, and, in the second, no injury severe enough to produce any change in the veins was recorded. As is so often the case, trauma evidently called attention to a lesion already existent but hitherto unnoticed.*

* Just how far this idea has been carried that trauma is at the basis of some of these lesions is illustrated by the use that Cushing[13] made of the term. He wrote: "Two cases of this sort, traumatic in origin, have come under my observation at the Johns Hopkins Hospital. In one of them not only was there a central swelling present but large dilated vessels radiated from it to the frontal and occipital regions. In both the process was associated with a slow-growing brain tumor, and the intracranial stasis had presumably led to a widening of an emissary vein and the production of a dilated venous sac in the midsagittal line. The swelling disappeared in both cases when the circulatory condition had been readjusted by a decompressive craniectomy." Since this statement was published in 1919 and never further explained, it is uncertain whether Cushing described the venous medusae which are so typical of parasagittal meningiomas or whether he described a true sinus pericranii provoked to activity by an increase in intracranial pressure, a development without counterpart known to the writers. At any rate, Cushing's use of the term "trauma" in this connection is not comparable to the connotation given it by contributors to the subject of sinus pericranii.

The trend toward the assumption that the great majority of cases are to be accounted for on a congenital basis is perhaps the modern one. A study of the lesion in the few cases which have come to autopsy or in which the nature of the malformation could be studied at operation seems to indicate that the enlarged veins are typical varices as are found in other portions of the body. If all this is true, the introduction of the third or "spontaneous" group is not important, if not actually unnecessary. Simply because some of the lesions have become apparent at some interval after birth does not exclude the fact that they are in fact congenital. As a matter of record, it seems that the great majority of the racemose or varicose form (Mastin) make their appearance apparently *de novo* during childhood or even later.

From the standpoint of pathology it seems more accurate to attempt to classify the lesions on the basis of their anatomic structure. Since in particular this classification also suggests the etiologic factor responsible, the classification introduced by Heineke has much to recommend it. It may be stated as follows: (1) varix herniosus sinus sagittalis, a congenital bulging of the sinus sagittalis through an opening in the skull; (2) varix communicans, as (a) varix simplex communicans, an excessive congenital enlargement of a single large vessel, and (b) varix racemosus communicans, a congerie of congenitally enlarged veins; and (3) a varix spurius communicans, the traumatic lesion which results from a fracture or other defect in the skull through which an abnormal venous communication develops. On this basis it is recognized that the varix simplex and the varix racemosus may exist from birth (the original "congenital" type) or may appear during later life and after a variable interval (the so-called "spontaneous" type).

With this introduction the nature of the lesion itself may be investigated.

THE STRUCTURE OF SINUS PERICRANII

While the lesion herein designated as sinus pericranii is recognized to be a congenitally enlarged vein or veins, the internal structure is not always identical. This is suggested by the above classification which recognizes three separate entities, one of which, the congenital, is subdivided on the basis of the size and number of abnormal veins involved. It is necessary to consider each type separately.

Varix herniosus sinus sagittalis. In this group are included the examples of saccular outpocketings of the sagittal sinus which protrude through the skull in the vicinity of the original posterior fontanelle. They are evidently the end result of a persistent large communication between the intra- and the extracranial venous systems. Their almost exclusive location in the occipital region would suggest that their persistence has something to do with the closure of the posterior fontanelle, but there may indeed be some additional factor as yet unknown which may play some additional rôle. The fact remains that the lesion is a venous sac which has a more or less wide communication with the superior longitudinal sinus. In some instances the sac is of about equal diameter throughout its length; in others there is a definite constriction of the portion which passes through the bone. Its relationship to the more common form of sinus pericranii is indicated by those cases in which the communication is small or in which mul-