

THE INTERSTITIAL TISSUE
of the
CENTRAL NERVOUS SYSTEM
with especial reference to the
CLASSIFICATION OF GLIOMATA

by

JAMES K. SLATER, M.B., Ch.B.



PREFACE.

The objects of the research embodied in this Thesis were, firstly, to determine the exact nature of neuroglia, secondly, to observe its behaviour under abnormal conditions, and thirdly, from the material analysed, to make certain observations upon the modern nomenclature and classification of gliomata.

It is a very great pleasure to record my indebtedness and gratitude to many colleagues in the Royal Infirmary, but especially to Professor Edwin Bramwell and Dr. Alexander Goodall for so generously allowing me to make use of cases which came under their care. My interest in the Pathology of the Nervous System was originally stimulated by Dr. F. E. Reynolds, and his able guidance has always been most willingly given. The facilities for the animal experiments were most courteously given by Sir David Wilkie, and were carried out in the Surgical Research /

Research Department. Lastly I should like to acknowledge my indebtedness to Mr. John Grieve for his faithful reproductions of the preparations illustrated in colour.

It seems probable that the interstitial tissues are an important factor in the process of nutrition of the nerve cells.

Before studying the method by which nutritive exchange of the cell is brought about, it is essential to be thoroughly conversant with the structure and arrangement of the elements concerned.

As the views at present held on the structure of neuroglia are widely divergent, an investigation, embodied in this thesis, was undertaken to ascertain which teaching I myself should follow.

It is well, first, to recapitulate briefly the points in the embryological development of the neural tube which are of importance in this study.

At a very early stage of embryological life, certain cells of the ectoderm become folded in as the neural groove. By further proliferation and /



Fig. I. - Microphotograph of a paraffin section cut transversely through a 124 hours' old chicken embryo, showing the general anatomy of the spinal cord, dorsal root-ganglia, and sympathetic ganglia. a, b, c, Ependymal, mantle, and marginal layers respectively of the spinal cord. d, Dorsal root-ganglion. e, Sympathetic ganglion. f, Notochord.



Fig. II. - Microphotograph of a frozen section im-
:pregnated by the silver method described:
taken from a 124 hours' old chicken embryo
and showing the same general structure as
in Fig. I., but with the dorsal root and
sympathetic ganglia more emphasised.

and invagination, the groove becomes converted into a hollow tube. From the cells composing the walls of this tube are developed the parenchyma and the greater part of the interstitial cells of the central nervous system.

Soon the cells of the neural tube arrange themselves into three distinct layers or zones.*

1. The Innermost or "Ependymal" Layer:- This is composed of large rounded cells with nuclei rich in chromatin. In sections of the tube some of the cells are seen to be undergoing mitotic division, and to these the name of "germinal cells" has been given. Division of cells, that is, the so-called germinal cell, occurs only in this zone.

Certain of the cells of this layer later become differentiated into the ependymal lining of the ventricles of the brain and of the central canal /

* Fig. I. Fig. II.

canal of the spinal cord.

2. The Middle or "Mantle" Layer:- This is composed of cells derived from the germinal cells. They are of three distinct structural types. (a) The neuroblasts are large cells resembling those of the ependymal zone but which have developed processes, namely, the primitive axon and dendrons, and which later become the neurocytes or nerve cells.

(b) The spongioblasts are columnar in type and their nuclei are much smaller than those of the neuroblasts; these cells are the precursors of the neuroglial cells. (c) The remaining cells are similar in appearance to those of the ependymal layer, and histologically have not yet differentiated into neuroblasts or spongioblasts; they are called, therefore, "indifferent cells" and represent a stage in the development of two fully differentiated elements. /

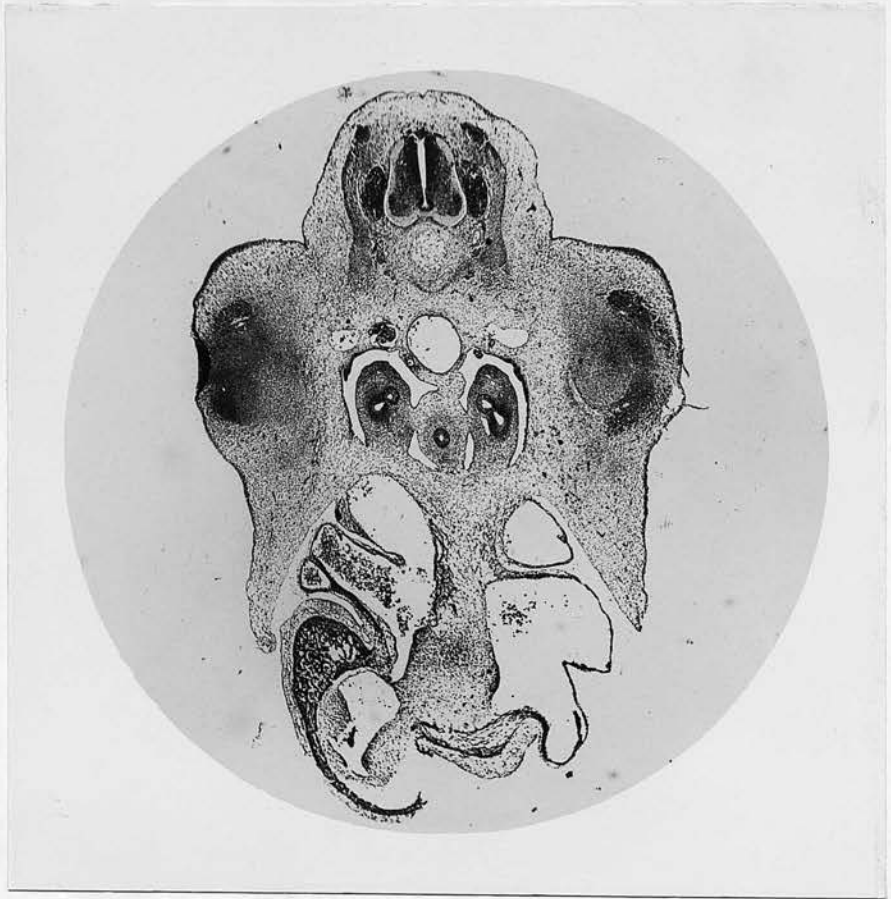


Fig. III. - Microphotograph, low power, from same preparation as Fig. I., showing the relationship of the spinal cord to the remainder of the developing embryo at that stage.

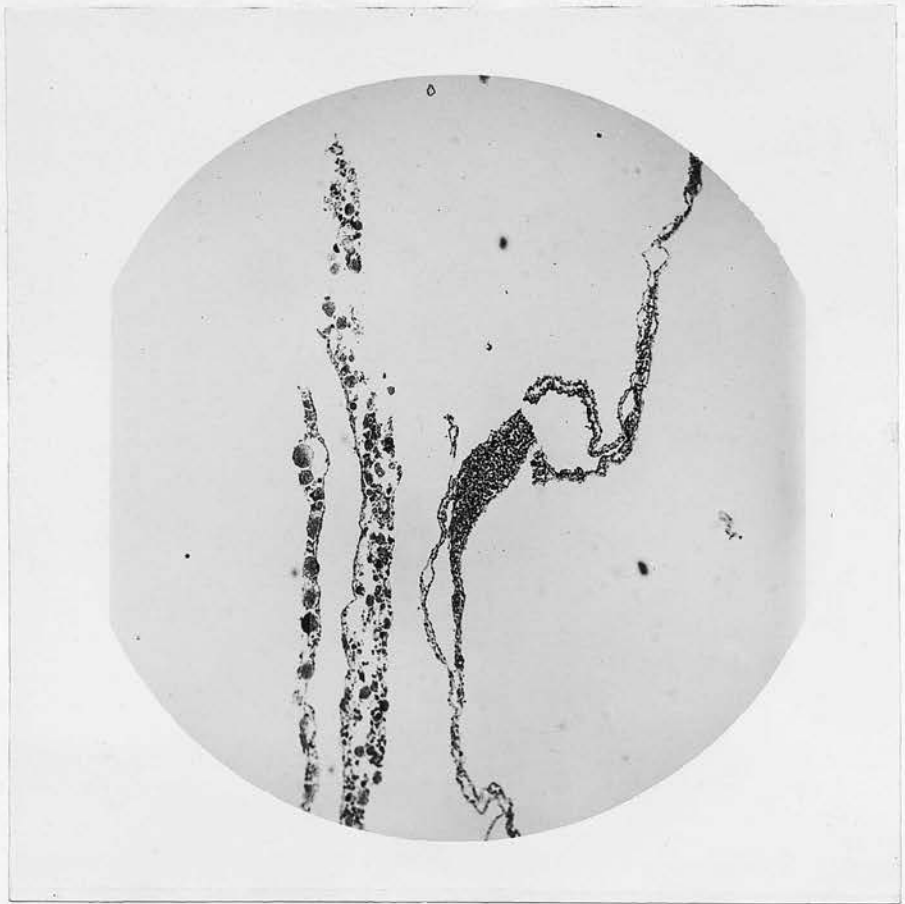
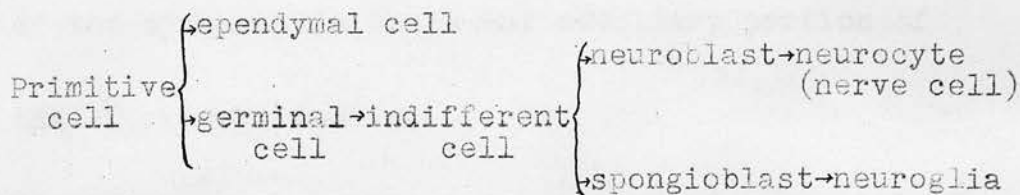


Fig. IV. - Microphotograph of a paraffin section cut transversely through a 36 hours chicken embryo, showing the neural ridge already developing.

elements. Indifferent cells may persist as such or develop into neuroglia or, during prenatal life, into neuroblasts.

3. The Outer or "Marginal" Layer:- This consists of processes of the spongioblasts of the mantle layer.

The development processes may be summarised in the following scheme:-



There remains to be considered the development of the nervous ganglia, namely, the dorsal root-ganglia and the sympathetic ganglia including the medullary portion of the suprarenal body.*

When closure of the neural tube is complete, it is connected to the surface ectoderm by a longitudinal ridge of cells called the neural crest.** This soon becomes separated from the

surface /

* Fig. III.

** Fig. IV.

surface ectoderm, but remains attached to the dorsal portion of the neural tube and from it, by a process of budding, are formed the cranial and spinal sensory root-ganglia.

The ventral portions of the spinal ganglia, from the level of the first thoracic downwards, separate off from the main mass and form the ganglia of the sympathetic chain and medullary portion of the suprarenal bodies.

Historical:- By the introduction of a special method of metallic impregnation,* Golgi (1873, 1885)^{1,2} was the first to demonstrate satisfactorily the structure of neuroglial cells. His method gave a silhouette picture of the neuroglial cell and depicted it /

* The essential difference between staining and impregnation is that in the former the colouring matter enters into molecular combination with the stainable tissue, whereas, in impregnation, the metal is precipitated on the surface of certain selected cells and tissue components.

it as stellate in form (astrocyte). He described two main types; in the first, which was that more commonly found, the cell possessed long, fine, unbranched processes (fibrillar or spider cells); in the second, the processes of the cell had numerous branches which terminated near the cell body (arborescent or protoplasmic cells). He recognised the neuroglia as composed of separate and distinct cells with processes which penetrated between the nervous elements.

As the outcome of much work, Weigert (1895)⁵ introduced a staining method which was specific for neuroglial fibres, and by this he demonstrated with greater clearness the fibrillar elements of the neuroglial cell. It is to Weigert's studies that we owe much of our knowledge of the nature of neuroglial fibres and their relationship both to each other /

other and to the nucleus of the cell. He taught that the fibres were developed either in the cell or under its influence, and that later they were completely separated from its cytoplasmic body and came to lie free. This conception of the development of neuroglial fibres was similar, therefore, to what is known to occur in the case of fibrous tissue.

The chief disadvantage of Weigert's method of staining were, that it was capricious even in his own hands, and that it could be used only on human tissue. Moreover, although by this method the nucleus was stained in addition to the fibres, the cytoplasm was not stained; since Weigert never succeeded in combining a cytoplasmic stain with his specific method, he concluded that the neuroglial nucleus was surrounded by so thin a film of cytoplasm that it was not demonstrable.

Weigert's work led to much investigation on the structure of the neuroglia. A great deal of this research was directed towards demonstrating the cytoplasm of the cell in addition to the nuclear and fibrillar elements.

In connection with this work, special mention must be made of that of Hardesty (1902)⁴ and Held (1903).⁵ These workers maintained that the syncytium formed by the spongioblast of the neural tube, as described by His, was retained permanently by the neuroglia. According to them, the neuroglia was composed of a richly branched cytoplasmic syncytium, at the nodes of which were embedded nuclei, and which was strengthened as a supporting element by the development in it of fibres. As a result of this conception of the structure of the neuroglia, Held suggested that the neuroglial /

neuroglial cytoplasm formed a pathway for the nutrient exchange between the lymph-vascular systems* and the functional nervous elements. It will be noticed, therefore, that an important distinction between the teaching of the two schools of Weigert and of Hardesty and Held was, that the latter maintained that the fibres were intracellular, whereas according to Weigert they were extracellular.

The present day conception of the structure of neuroglia is founded very largely upon Golgi's original silver impregnation methods and is associated with the names of Cajal, Hortega, Penfield,^{6,9} and others of the "Spanish School." My own investigations have led me to accept their teaching.

Stated /

* In the brain and spinal cord there are no closed lymph channels. The lymphatic system is composed of the clefts ("Virchow-Robin spaces") between the connective tissue fibrils and cells which form the adventitia of the blood vessels. The membrana limitans perivascularis and the external adventitial layers are closely welded together, there being no space between them.

Stated briefly, neuroglia consists of separate individual cells; the fibres are intracellular; and the cells consist of several types.

Cajal¹⁰ separated the cells of the central nervous system into three components:-

1. The nervous parenchyma.
2. Astrocytes, some of which contain fibres, "fibrous astrocytes," and others which do not contain fibres, "protoplasmic astrocytes."
3. Cells differing structurally from the astrocytes in that they possess no processes, and which he named "the third element of the central nervous system" (1913).

Later Hortega (1921)¹¹ showed that the cells comprising "the third element" of Cajal actually had processes, and he differentiated this group into two types, according to their structure and what he believed /

believed to be their origin and function. These types he named (a) oligodendroglia and (b) microglia.

I propose to consider in greater detail these types of interstitial cells and to deal not only with their structure and distribution, but, so far as our present day knowledge allows, with their function.

It may be mentioned here that certain functions common to all the interstitial cells of the central nervous system have been suggested. Of these, it is certain that the cells act as the supporting structure of the nervous parenchyma.

Further, certain authors believe that the interstitial tissues may act as an insulating medium preventing dispersion of nervous impulses to neighbouring paths. Again, it has been maintained that the resilient nature of neuroglia may protect the delicate nervous tissue from the pulsations of the blood /

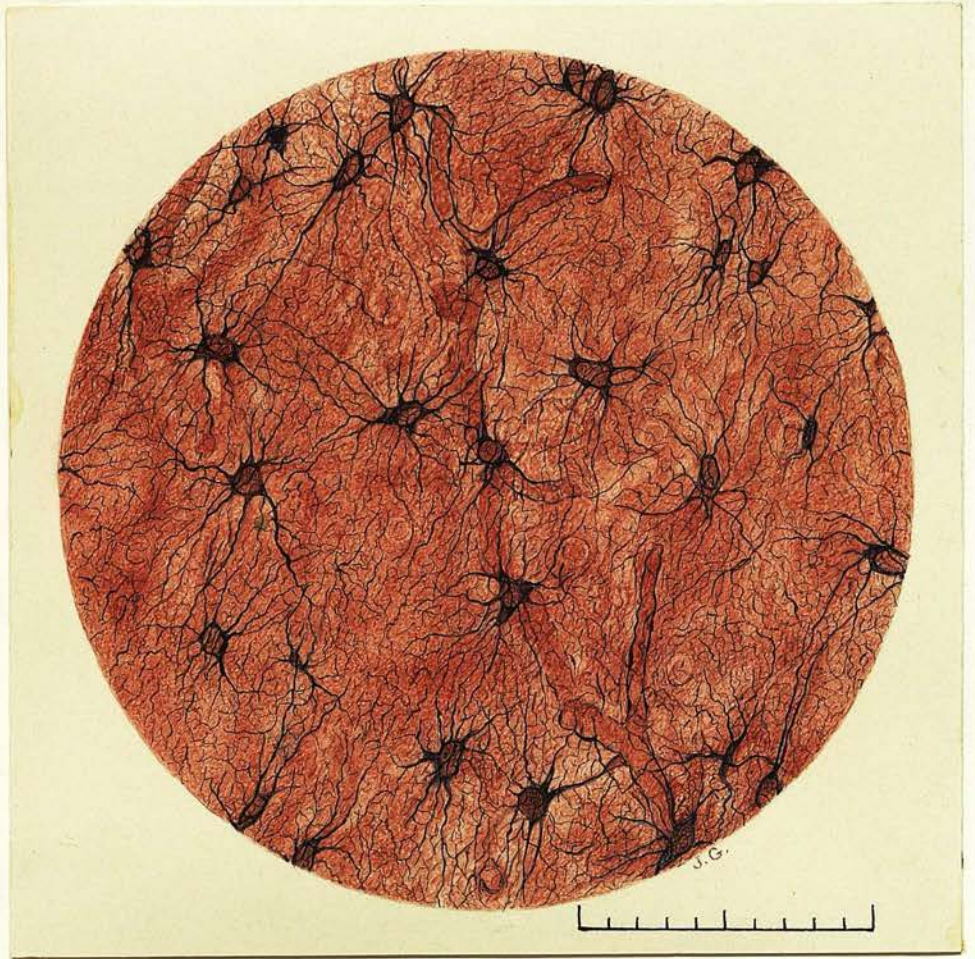


Fig. V. - Coronal section through the white matter subjacent to the cerebral cortex showing the distribution of astrocytes. The cells are fibrillar in type and in several instances a process is seen terminating in a vascular foot-plate.

(Section treated by Cajal's gold sublimite method.)



Fig. VI. - Coronal section through the white matter subjacent to the cerebral cortex showing the fibrous type of astrocyte. Many of the fibres can be traced from one process into another sweeping past the nucleus as they pass through the perinuclear cytoplasm. One of the processes is short and thick and terminates in a vascular foot-plate implanted upon the adventitial wall of a capillary.

(Section treated by Cajal's gold sublimate method.)

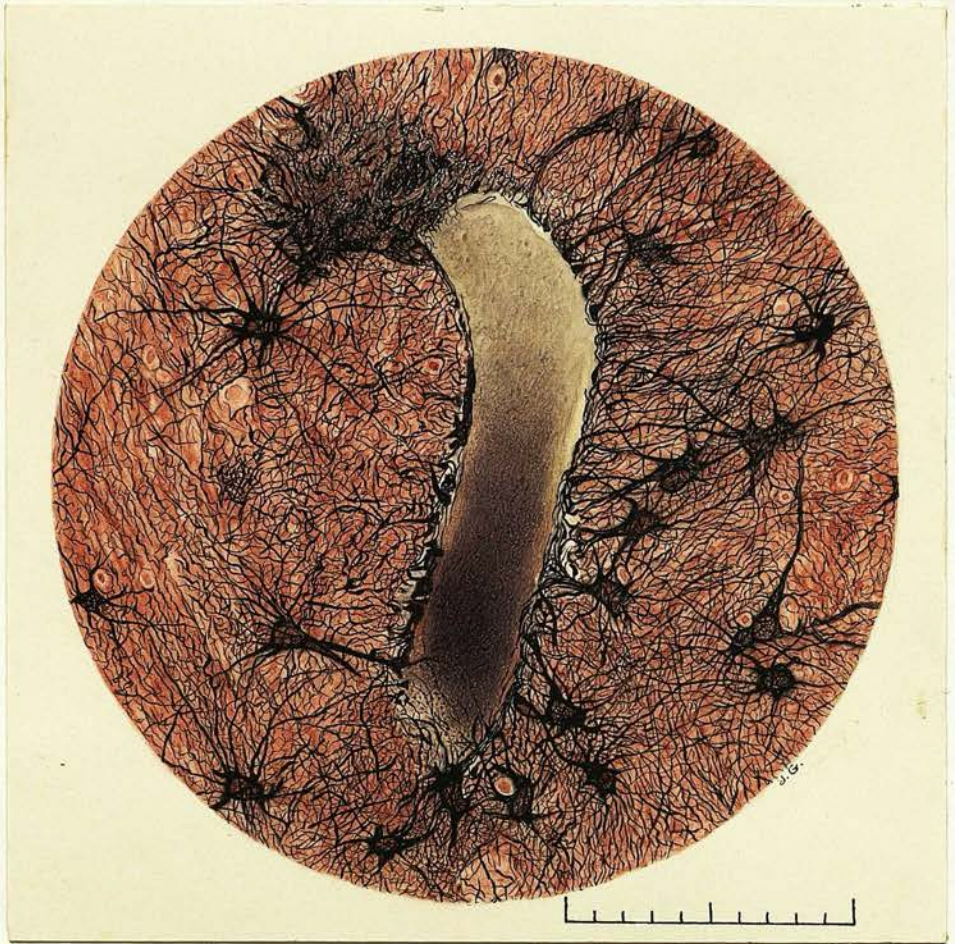


Fig. VII - Coronal section through the white matter subjacent to the cerebral cortex showing the composition of the membrana limitans perivascularis around a small blood vessel. The membrane is formed by fibres and vascular foot-plates of astrocytes

(Section treated by Cajal's gold sublimate method.)

blood vessels.

Astrocytes:- As already noted, astrocytes are of two types, namely, those containing fibres, and those having no fibres developed in their cytoplasm.

Both types of cells are large and have many processes. These vary in length; many of them can be traced for considerable distances from the perinuclear cytoplasm, others are shorter. At least one of the processes of every astrocyte is implanted upon the adventitial wall of a capillary or smaller blood vessel. The implantation takes the form of a small pyramidal expansion of the cytoplasmic process and is known as the "vascular foot-plate".* The length of the process concerned depends naturally on the situation of the cell relative to the blood vessel. Where the process is short, it is usually of considerable diameter.** The nucleus is large, relative /

* Figs. V., VI., VII. ** Fig. VI.

relative to the perinuclear cytoplasm, spheroidal and rich in chromatin.

Most authors agree that both types of astrocytes have the power of multiplying by amitotic division.

In the "Fibrous" type of astrocyte the fibres vary in length and thickness and some of them may be traced for a very considerable distance away from the cell body. The fibre distant from the cell body is covered by so thin a film of cytoplasm that the envelope is little more than a prolongation of the cell membrane. The fibres have no free ends in the perinuclear cytoplasm;* each individual fibre may be traced from one process into another, sweeping past the nucleus as it passes through the perinuclear cytoplasm. In no instance has a fibre been traced from one astrocyte into another.

On /

* Fig. VII.

On the surface of the central nervous system the neuroglia is condensed to form a limiting membrane (*membrana limitans superficialis*). As the blood vessels penetrate into the central nervous system from the pia mater they carry with them a prolongation of this superficial limiting membrane (*membrana limitans perivascularis*), and thus everywhere the vascular tissue is definitely separated from that of the cerebrospinal substance. The strength and consistence of this condensation of neuroglia is due to a rich development of neuroglial fibres and, in the case of the *membrana limitans perivascularis*, of vascular foot-plates.*

Astrocytes are present throughout the whole of the grey and white matter of the central nervous system. The majority of the astrocytes in the grey matter are of the "protoplasmic" type; in the /

*Fig. VII.

the white matter and in the membranæ limitantes the "fibrous" type largely predominates.

One undoubted function of the astrocyte is to support the nervous parenchyma. That every astrocyte should have a process which brings it into relationship with the lymph-vascular system and that the process should be expanded into the structure already described as a "vascular foot-plate" is a fact very significant in regard to the nourishment of the cell. It seems highly probable to me that the foot-plates are developed to give a greater absorbing or excreting surface and that they subserve the function of nutritive exchange between the astrocytes and the perivascular spaces. Moreover, such a thesis does not depend upon the presence of a syncytium since each individual astrocyte is in relation to a blood vessel and its accompanying lymph /

lymph spaces.

Further, if the vascular foot-plates sub-
serve the function of nutritive exchange between the
astrocytes and the perivascular spaces, it seems
possible also that the nutrient exchange of the
nervous parenchymal cell may take place through the
astrocyte, as suggested by Held (vide supra). Ana-
tomical support of such a theory could be advanced
from the fact that in those areas in which the so-
called bodies of the nerve cells occur, namely in
the grey matter, the majority of the astrocytes are
"protoplasmic" in type. This type of cell cannot
give such good structural support as the "fibrous"
type but it seems justifiable to suppose that it would
form a better channel for the passage of nourishment
than would the cell in which so much of its cytoplasm
has been differentiated into fibres. The "fibrous"
type /

type, moreover, occurs in areas in which the need for support predominates over that for nourishment, namely on surfaces and in the white matter.

In each situation, the requisite need for support and for nutrition may be provided for by the minority of the astrocytes present, namely the "fibrous" and "protoplasmic" types respectively.

Oligodendroglia:- The oligodendroglial cell is smaller than the astrocyte and, as its name implies, has few processes; moreover, the processes are not so long as in the former type of neuroglial cell. Most of the cytoplasm lies at the bases of the larger processes; the cell does not possess any fibres nor do any of its processes terminate in a vascular foot-plate. The nucleus is comparatively small, but its chromatin is large in amount and therefore compactly arranged.

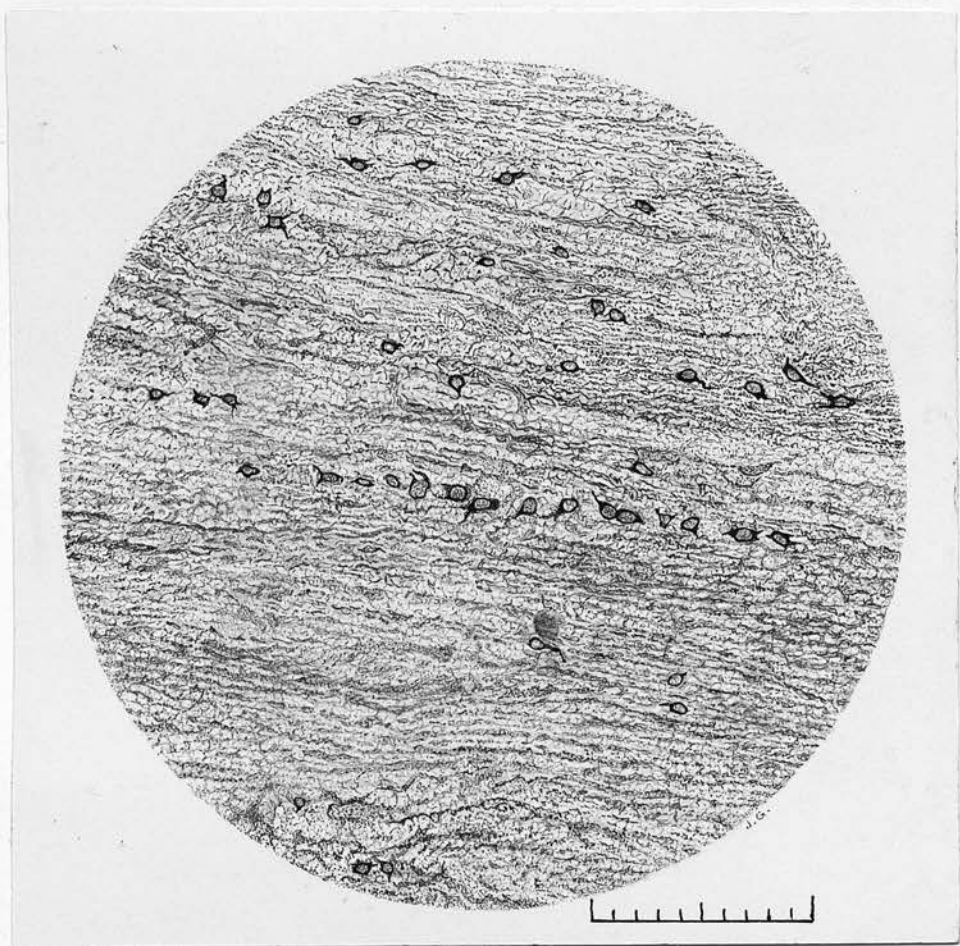


Fig. VIII - Longitudinal section through the spinal cord of the adult dog, showing oligodendroglia. The cells have few processes and some of them are arranged in rows.

(Section treated by Hortega's silver carbonate method for oligodendroglia)

Oligodendroglia occurs between the myelin sheaths of nerve fibres and hence it is often seen in rows in the white matter.* A certain number of small oligodendroglial cells occur in the grey matter where they act as "satellites" to nerve cells, their processes wrapping themselves around the parenchymal cell.

Oligodendroglia is very abundant and comprises the majority of the interstitial cells of the central nervous system. It is plentiful in young animals, especially during the period of maximum myelinisation, and at this time the cells are particularly rich in granules. From these two facts many authorities believe that this type of cell is concerned in the secretion of myelin around the nerve fibres within the central nervous system. Further, from this anatomical relationship to /

* Fig. VIII.

to the nerve fibre, it has been suggested that there is an analogy, both structurally and functionally, between oligodendroglia within the brain and cord and the neurolemma which envelopes the myelin sheath of the peripheral nerve fibre.

Oligodendroglia is not an immature form of astrocyte; it is a specialised neuroglial entity, and in specialisation has lost the power of reproduction.

In passing, it should be mentioned that oligodendroglia having the normal histological structure is seldom seen in human post-mortem material. It very rapidly undergoes autolytic changes as a result of agonal and post-mortem processes.

It is interesting to note that, in 1900, Ford Robertson¹² described certain cells which he believed to be of mesodermal origin and which he named "mesoglia." It is now known that these are /

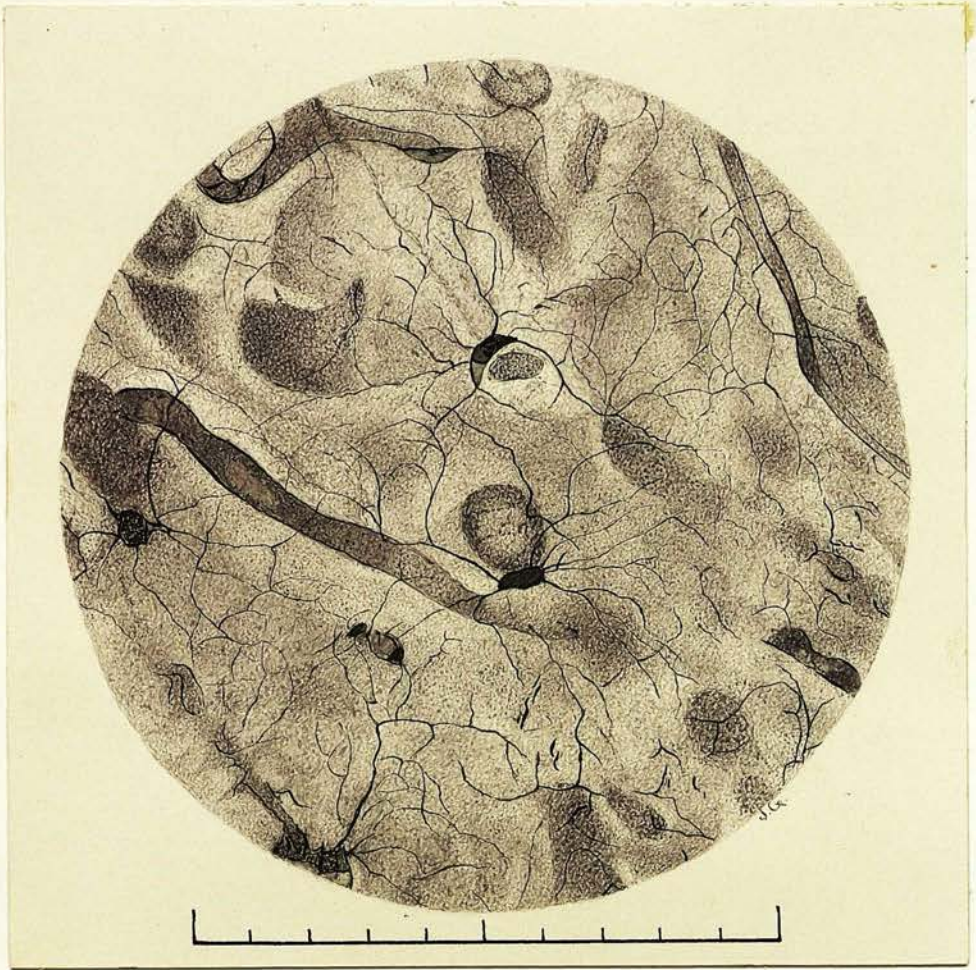


Fig. IX. - Horizontal section through the cerebral cortex showing microglia. The arrangement of the processes causes many of the cells to appear bipolar and typically the nuclei are elongated. Near the centre of the field are two faintly-stained nerve cells, each of which has a microglial "satellite".

(Section treated by Hortega's silver carbonate method for microglia.)

are the cells designated oligodendroglia and that they are ectodermal in origin.

Microglia:- These cells are comparatively small. Their cytoplasmic processes, which have numerous branches, are frequently so arranged as to give the cell a bipolar appearance. The cells possess neither fibres nor vascular foot-plates. The nucleus is small; typically it is elongated in shape and contains a relatively large amount of chromatin.*

Microglial cells are found throughout the central nervous system, but are more plentiful in the grey than in the white matter. A few of the "satellites" of the nerve cells are microglia, the majority, however, being oligodendroglia.

Hortega maintains that the microglial cells are mesodermal in origin, and his view as to the origin of these cells is accepted by Penfield although /

* Fig. IX.

although the actual transition from the mesodermal cell to the microglial cell has not yet been demonstrated.

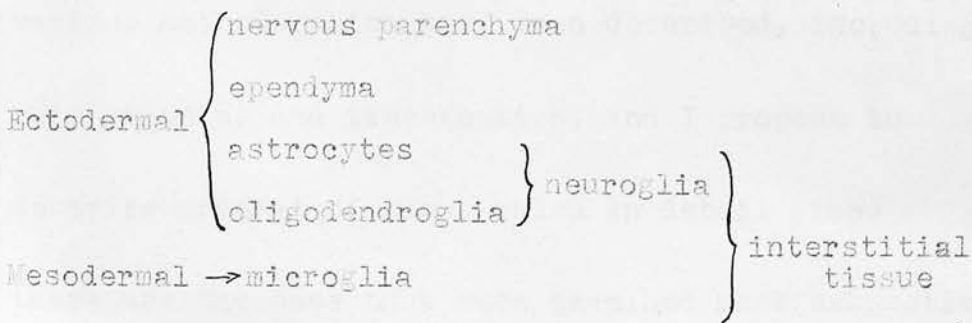
Microglial cells are few in number up to near the time of birth; at birth and during the first few weeks of post-natal life, they increase very rapidly. They are believed to be derived, chiefly at any rate, from the mesodermal tissue of the pia mater in the neighbourhood of its invagination to form the choroid plexus and from the pia mater covering the under surfaces of the cerebral peduncles.

From these sites, the microglial cells spread through the white into the grey matter, and after some months are more numerous in the latter.

Microglia may become wandering amoeboid cells; it is believed that they are the chief elements concerned in phagocytosis of particles of cerebral /

cerebral tissue after destructive processes such as occur in cerebral softening, and in their removal to the perivascular lymphatic spaces.

The following scheme shows the origin and relationship of the elements of the central nervous system:-



Under the term "gliosomes" several authors have described small rounded bodies occurring within astrocytes and oligodendroglial cells and which they maintain are specific for neuroglial cells. This question has not been dealt with in this thesis since I have not yet convinced myself as to the nature and significance of these bodies.

Having /

Having now made up my mind as to what constituted the individual elements of the interstitial tissue of the nervous system, I decided to investigate a number of cases of gliomata in order to determine what classification of these tumours I should follow. Some twenty-five cases were carefully examined by the various methods which have been described, including both staining and impregnation, and I propose to describe several of these cases in detail since these are the ones that were examined most exhaustively, and since the clinical features of the cases have an important bearing on the thesis I propose first of all to discuss certain of the outstanding clinical aspects in order that the interpretation of the individual cases may be more clearly understood.

Clinical Considerations:- The study of neurology cannot /

cannot be pursued for long before attention is occupied greatly by intracranial tumours of the central nervous system. The reason for this is that much of the present day knowledge of cerebral and spinal function has been acquired by careful observation of symptoms and signs produced by neoplasms in different situations of the central nervous system. Moreover, the accurate localisation of tumours has now, more than ever before, become a matter of the utmost practical importance, since the onward march of neuro-surgery has been so markedly rapid. To the inexperienced clinician it may seem quite a simple matter to determine at what site interference with the nervous function is occurring; it cannot, however, be too strongly emphasised that much patient study and assessing of the phenomena presented is required before even a /

a moderate degree of skill is attained in localising the site of the tumour. Thus, while the grosser manifestations of disease may be evident, it is only after much experience that it becomes possible to separate the signs which are of importance from those which merely cloud the picture. The basis of this experience must of necessity be made at the bedside, and no amount of reading can replace the knowledge thus gained. We who live in a generation in which experimental method and methods of precision are being constantly held before us, are too often tempted to augment our deficient powers of observation by a too ready resort to one of these, and thus the modern tendency is to spend too much time in a study of radiograms and elaborate reactions of the cerebro-spinal fluid to the neglect of the more readily obtainable clinical facts of the case.

While /

While wishing primarily to emphasise the importance of bedside training, it is not desired to suggest that no place is to be found by the student of neurology for certain laboratory tests, but only to maintain that these must be regarded by him, in the first instance at least, as of merely confirmatory value.

In the nervous system, as in no other system in the body, is the student able from the very beginning of his clinical studies to correlate and to appreciate fully the training he has had in anatomy, physiology and pathology, because it is in dealing with nervous disease that he finds himself for the first time constantly referring to his knowledge of all three of these subjects. Although this truth applies to all forms of organic nervous disease, it becomes at once apparent when considering neoplasms /

neoplasms of the brain and spinal cord. Briefly stated, a clinical neurologist is essentially one who is well equipped with a knowledge of the preliminary subjects of the medical curriculum and who has studied patiently all the available clinical material for a period of years; all things being equal, his experience is directly proportional to the number of years he has practised.

Before any morbid condition can be prevented or before it can be treated rationally when once it is established, the clinician must have a complete understanding of the processes which constitute the particular disease. In this connection, the careful study of the manifestations of disease as exhibited by the patient has been emphasised. The researches of the clinician cannot, however, stop at the bedside while the patient /

patient is still alive. A valuable opportunity is given him of checking the observations made during life and of augmenting his understanding of the condition in those cases which terminate fatally. Frequently at autopsy anomalous signs and symptoms, phenomena which could not be explained with certainty during life, are made clear. Further, since disease is a condition of cells, cellular pathology, both anatomical and functional, must be studied by him. In many instances, the structural relationship of cells to each other, the anatomical changes in the individual cells, the presence of an excess of cells of a particular type may give information of the utmost value and from which may be deduced much of the process which was going on during life.

Hence to study fully disease, it is of primary necessity that the clinician makes his observations /

observations not only during life but at autopsy and later through the microscope.

The good fortune to make an original observation of fundamental value is only bestowed on the very few, but this does not mean that knowledge is not advanced by the aggregate of observations from many different sources; undoubtedly it is by this latter method that many of the important steps in medicine are taken. No clearer illustration of these facts can be seen than that demonstrated by the recent advances in the knowledge of the structure, mode of growth, and sequelae of brain tumours, particularly of those of the glioma group.

In spite of their importance, neoplasms of the brain are relatively infrequent. As in the case of all neoplastic growths, they occur at all ages /

ages, are found in every conceivable location within the cranial cavity, and vary greatly in their pathology. In these respects they differ from so many other organic nervous diseases. Previous to 1919 many extensive monographs had appeared, treating the subject from many different standpoints.

Notable among these are the contributions of Starr¹³, Von Monakow¹⁴, Oppenheim¹⁵, Tooth¹⁶ and Redlich.¹⁷ These authors dealt with a large series of cases and described tumours in almost every region of the brain. From this time down to the present day, however, the majority of authors have been more attracted to the surgical aspect of the problem and have concerned themselves largely with the question of dividing these neoplasms into two great groups, operable and non-operable.

Among recent studies which have taken up a more general /

general viewpoint, both clinical and pathological, are those of Edwin Bramwell (1921)¹⁸, Cushing (1922)¹⁹, Cushing & Bailey (1925)²⁰, and Purves-Stewart (1927)²¹.

In most of the published monographs and articles the authors deal with intracranial in contradistinction to intramedullary neoplasms. Moreover, since certain other conditions, for example, gummata and localised tuberculous lesions within the cerebral substance (so-called "tuberculomata"), parasitic cysts, give rise to clinical manifestations similar to neoplasms at the same site, it has been usual to include these under the terms intracranial and cerebral "tumours". However justifiable this may be on clinical and terminological grounds, it is apt to lead to confusion, and scientifically, so far as is known, lesions due to infective micro-organisms are in an entirely different category to neoplastic growths.

Further, metastatic neoplasms occurring in the medullary substance are included in the statistics of new growths of the brain and spinal cord.

It is not surprising, therefore, that statistics endeavouring to show the frequency of cerebral "tumours" and also of cerebral neoplasms in relation to other diseases of the central nervous system vary considerably. For instance in the Vanderbilt Clinique in America, out of 18,000 cases of nervous disease there were 48 brain tumours. Bruns²² states it as high as two per cent., but on the other hand Cushing²³ and Redlich²⁴ both give .75 per cent. Speaking generally, it would appear that if the average from all different sources was taken, it would be somewhere between these two figures. When we remember the very numerous different /

different types of tumour included, it will be readily understood that even the most prevalent form can only have a very small incidence indeed.

Certain teratomata, dermoids, angiomata have a congenital origin, and other very rare types can be explained as a result of developmental anomalies. Of neoplasms of the brain it is found that gliomata are the most frequent. They preponderate over any other class in adults. In Tooth's²⁵ summary of 500 cases from the National Hospital, London, 49 per cent. were gliomata. As the present series of cases show, gliomata occur throughout the brain or spinal cord as circumscribed or diffuse tumours; the general tendency, however, is towards diffuseness, and degeneration with hæmorrhage and cystic formation take place principally in intracerebral growths. Thus the symptoms /

symptoms, particularly of neoplasms arising in the hemispheres, are apt to develop intermittently.

Gliomata, as their name implies, arise from the neuroglial tissue or "glia". Undoubtedly the etiological factors responsible for them are of the same nature as those which cause new growths in general. These factors are unknown at the present time and it is outside the province of this thesis to discuss the various theories which have been advanced from time to time to account for neoplastic formations.

In this connection, however, mention must be made of trauma since this has been advanced by many writers as a causative factor in the occurrence of gliomata and was indeed a factor in one of the cases described below. The type of injury is usually quite trivial and it would seem reasonable to /

to suppose that in many instances this has merely focussed attention on a pre-existing state of affairs.

Clinical Manifestations:- Although gliomata may have a greatly varied structure, their behaviour from the clinical point of view is much more dependent on their anatomical localisation than on any other consideration.

It is important to recognise that symptoms, when these exist at all, belong to one or other of two classes; they are either focal or general.

The focal symptoms appear because of involvement of a particular area or region of brain; whereas the general symptoms are a manifestation of the compression to which the cranial contents as a whole are subjected by the growth of the neoplasm. It follows quite naturally that localisation is dependent /

dependent entirely upon focal symptoms, and difficulty arises when the general symptoms are of such a nature as to obscure in whole or in part the value of the localising ones. Moreover, it frequently happens that the focal symptoms remain absent or only appear at a much later date than the signs of increased intracranial pressure; on the other hand, however, the diagnosis may be quite apparent at a much earlier date than that of the onset of the general symptoms, although this is more especially the case with endotheliomata and neurofibromata. There can be no doubt that both these classes of symptoms are produced more by compression than by destruction of brain tissue, because as increased bulk of the brain arises, first cerebrospinal fluid and then blood are expelled from the cranial cavity, and it is from paucity of the latter /

latter that interference with function develops.

The development of the Jacksonian fits which sometimes accompany a neoplasm in the region of the cortex is due to the same mechanism, because it is a well-known fact that motor cells become more excitable when their oxygen supply becomes reduced, and when thus excited they are liable to discharge with the production of the well-known focal convulsion.

The general symptoms are indicative of the "tumour" as a whole, irrespective of its special nature or localisation. Although many different symptoms come under this group, the outstanding triad are headache, vomiting and papilloedema. Of lesser importance are such symptoms as nausea, dizziness, mental changes, sometimes drowsiness and different convulsive phenomena. When they are present /

present at all, these general symptoms have a tendency to be progressive, but often they vary in their intensity from time to time. Frequently they remain stationary and may in some cases even regress and disappear.

Headache:- This symptom is more commonly present than any other, and is as a rule an early sign. The headache usually starts more or less irregularly, is frequently intermittent in the early stages and later becomes persistent, being either dull or severe in type; if dull, periods of excruciating exacerbation occur. The brain itself is insensitive, and the headache is due to stretching of the dura mater and stimulation of sensory nerve endings in its structure. Only occasionally is it of value as a localising symptom, it being usually frontal or occipital and of no localising value. Frontal tumours /

tumours often give rise to occipital headaches and vice versa; right-sided tumours to left-sided headache and vice versa.

Vomiting:- This symptom is most frequently found in those cases in which headache is a marked feature and which are accompanied by other signs of great increase of intracranial tension. It has been usual to describe the vomiting as "projectile" in type and unassociated with nausea, but undoubtedly it is misleading to emphasize this character, since frequently the type of vomiting met with is indistinguishable from that found in other conditions, and indeed ignorance of this fact must sooner or later lead to failure in recognising the true significance of vomiting in the early stages of cerebral tumour. When present, vomiting most often occurs in the morning, and at times it is so persistent /

persistent as to lead to starvation, exhaustion and even death.

Failure of Vision:- This symptom is of the greatest importance in the diagnosis of cerebral neoplasm.

The actual diminution of visual acuity is preceded by changes in the optic nerve head which are so definite that they can be seen by the ophthalmoscope, and one ought therefore to consider this symptom more as a sign, because actually a very definite increase of intracranial tension has occurred before any noticeable defect of vision is to be observed.

A very large percentage of all patients show changes of the optic nerve, which vary largely, depending upon the grade of intracranial pressure and the size and location of the tumour. Those neoplasms causing intracranial pressure (those situated in the posterior fossa particularly) force the cerebro-spinal fluid /

fluid into the space between the optic nerve and its sheath; this causes a papilloedema or choked disc. It is only when this "Choked Disc" becomes very pronounced that vision begins to fail, and as in most instances the development of a marked papilloedema is spread over a period varying from days to months, the advantage of using the ophthalmoscope in every suspected case must be at once apparent.

The failure of vision may be gradual, proceeding by an increasing peripheral constriction of the visual field, or it may be of dramatic suddenness. After blindness has ensued, the pupils tend to dilate and to become immobile.

Among the less common indications of an abnormally raised intracranial tension are a slowing of the pulse rate, which may fall as low as fifty or less per minute, an associated rise in the blood pressure /

pressure, and abnormality of the respiratory rhythm. There is also very frequently a progressive dulling of mental alertness, which passes on to stupor as the pressure within the skull rises. In any situation a cerebral neoplasm may give rise to sudden transient loss of consciousness with or without generalised convulsion. Such fits, however, have no localising value. Focal or Jacksonian fits, on the other hand, are most often of localising significance.

Each one of these general symptoms which have been discussed may vary greatly in intensity in different cases; all may be absent until the terminal stages of the illness. As a rule general symptoms occur with greatest intensity in rapidly growing gliomata, and most particularly in neoplasms situated in the posterior fossa of the skull. On the /

the other hand they are minimal in very slowly growing gliomata and in aged persons. It is important to remember that the clinical combination of headache and vomiting which may precede any loss of vision (though not the optic neuritis which ultimately produces it) may be observed in individuals whose general state of health appears good and who do not seem seriously ill. Thus there is frequently a failure to appreciate the possibly sinister significance of this symptom-complex, with the resulting omission to examine the fundi of the eyes, and an unfortunate delay before the correct diagnosis is made.

Focal Signs:- Before discussing the localising signs of disease of the brain it is necessary to describe the various ways in which a lesion may disturb the functions of the nervous system. It is a well recognised /

recognised fact that the activities of any part of the nervous system which is directly involved in a focus of disease may be influenced in either of two ways. They may be diminished or abolished on the one hand, or they may be stimulated to an excessive degree on the other. To cite a common example - a lesion involving the central motor cortex may by stimulation give rise to a focal or Jacksonian convulsion, or alternatively by destroying its nerve cells produce motor paralysis. Further, it is a common experience to find both these effects combined, a localised fit being followed by motor weakness. The terms paralytic and irritative are descriptions of these two forms of symptoms. Moreover, the central nervous system shows a high degree of local specialisation of function, yet normally it acts as a whole, and interference with any /

any one part of it may be followed by disorder of function in regions left untouched by disease. The fact can be easily understood when one considers the intimate anatomical association and the consequent physiological relationship of all parts of the central nervous system. Disorders of this kind are said to be indirectly produced and like those directly caused are of two orders. Thus when a hæmorrhage occurs in the internal capsule, the direct result of the lesion is a hemiplegia, but in addition there is a sudden loss of consciousness. The latter is an expression of the derangement of the whole cerebral equilibrium resulting from the functions of both cerebral hemispheres being disorganised as a result of the gross destructive lesion. When a hæmorrhage is the cause, the coma as a rule continues until death ensues; on the other /

other hand, when the disturbance of cerebral equilibrium has been caused by embolism or thrombosis the "shock" passes off, all parts of the cerebrum not actually destroyed resuming their activity with the hemiplegia remaining as a more or less permanent residuum. But the hemiplegia undergoes a curious change in type: whereas at first it is flaccid, in course of time it becomes spastic, that is to say, the muscles which have lost voluntary power begin to develop an excessive tonus and show an exaggerated type of tendon reflexes and the extensor type of plantar response. All these phenomena indicate that certain neurons released from the controlling influence of the others destroyed by the lesion are in a relative state of hyper-activity. It is therefore convenient to regard the symptoms of disordered action of the nervous system as belonging to /

to one of four groups. Of these groups, two are directly produced by the lesion, the remaining two being indirectly produced. In the former the symptoms are either irritative or paralytic, in the latter either shock or release. Further, it will be at once understood that of these, symptoms due to shock and irritation tend to be transient, while those resulting from distention or release may persist indefinitely. Certain other factors controlling the impairment or dissolution of function need only be referred to briefly. Thus the general law that lesions produced acutely cause usually more intense and extensive disorders of function than similarly localised and extensive lesions of gradual development, applies equally to the nervous system as to the other systems of the body. Again, when a glioma is causing dissolution of a high grade function /

function, the most recently and highly developed aspects of that function are impaired at an earlier time than its older and simpler components. For example, in a hemiplegia due to involvement of the motor projection fibres by a glioma, the isolated and skilled movements of the fingers are more severely impaired than the simpler movements common to the proximal parts of the arm. Again in that complex motor function, articulate speech, the power of expressing thought may be the first to be impaired and later lost. Finally, it must be realised that the central nervous system is dependent to a considerable extent on the quality and quantity of its blood supply. The nerve cell in particular is peculiarly sensitive to oxygen starvation, being stimulated at first and then paralysed as the oxygen drops below normal. The convulsions of asphyxia and /

and those which may accompany sudden profuse hæmorrhage into the peritoneal cavity are examples of the hyper-excitability developed by the cell at a certain level of oxygen deficiency and the ensuing coma is due to a complete cessation of function from a more severe oxygen deprivation. It is also quite probable that the Jacksonian fits produced by compression of the cerebral motor cortex by a glioma are brought about by vascular disturbance of this kind and not, as is so often stated, by direct mechanical stimulation of the cortex.

The Localising Signs of Glioma:- It now follows from what has been said about the different ways in which a glioma may disturb the functions of the nervous system that not only the localisation of the pathological process but also the rate of progressive destruction of nervous parenchyma may be expected to play a part in determining the character of the symptom /

symptom-complex, but actually it is the situation of the lesion which is the determining factor in the production of the symptoms. As a rule, the more rapidly the glioma grows, the greater is the disturbance of function to which it gives rise.

Conversely a slowly developing neoplasm may be completely masked for a long period by the development of functional compensatory activities in undamaged regions of the brain. Thus, whereas a hemorrhage in the neighbourhood of the internal capsule will at once produce gross disturbance of cerebral function, a slowly growing glioma in this situation may reach a considerable size before definite signs of pyramidal involvement develop.

Further, as will be brought out in several of the cases described, it is important to emphasize that the period in the clinical course of a given case /

case at which localising signs appear is of great importance in assessing their value. Unquestionably those which develop early have definite localising value, whereas the steady rise of intracranial pressure which accompanies the growth of the majority of gliomata causes widespread compression and resulting defect in the circulation and therefore of the function in regions of the brain remote from the neoplasm. It is in this way that "false localising signs" may become apparent in the later stages of the disease. The most frequently observed sign of this category is paralysis of the 6th cranial nerve, due undoubtedly to the long intracranial course which this slender nerve runs. As intracranial pressure increases, the contents of the posterior fossa of the skull, the cerebellum and brain stem, tend to be forced downwards towards the foramen magnum /



magnum, and in consequence the nerve is stretched tightly over the sharp edge of the petrous bone, and conduction along its fibres is interrupted. Should, however, an abducens palsy appear among the initial symptoms of glioma, it would indicate direct involvement of either the nerve or its nucleus by the neoplasm, and thus be of localising value.

When glioma involves those cortical areas which stand in close functional relationship with the projection fibre systems - motor, sensory and visual - it may be expected to give rise to recognisable localising signs. On the other hand negative information may be of value since there are large association areas which are silent in the sense that disease within them produces no focal symptoms. Hence in the presence of general indications of a glioma and an absence of focal symptoms the involvement /

involvement of a "silent area " of the hemisphere may be indicated. It is in such instances that by a process of exclusion the site of the neoplasm can be localised.

In this series of cases there are found a number of outstanding examples which illustrate many of the clinical points discussed and also emphasises the noteworthy and interesting features of the pathology. It is proposed now to discuss these cases in some detail and later to reconcile the lessons learned from them with the others in the series.

It is noteworthy that three of the series were gliomata in the cervical portion of the spinal cord, a situation in which these neoplasms are relatively /

relatively uncommon. Two of these cases occurred in hospital, one in private practice; each was thoroughly investigated clinically and all were operated upon; in the case of the hospital patients complete and detailed pathological investigations were made, but in the case of the third patient it was only possible to examine histologically the material obtained at operation. The following record brings out clearly the features of these cases and especially the pathological lessons that they provide.

W.D., male, aged 31, a motor mechanic, first consulted Professor Edwin Bramwell on October 20, 1927. The patient had been well until a couple of months previously; he then began to have some pain about the left shoulder, which he was inclined to attribute to a twist while winding up the engine of his car. The pain had gradually got better, but the upper part of his left arm had slowly become weaker; a little later he noticed that the right arm was becoming affected; the weakness in the arms increased progressively. The deltoids, the biceps and infraspinati muscles on both sides showed pronounced weakness with accompanying wasting. The upper parts of both trapezii, the sternomastoids and the pectoral muscles were acting well, but on the left side the action of the lower part of the trapezius was defective. The movements of the hands and of the wrists were unimpaired. On the thumbs, index fingers /

fingers and outer sides of both fore-arms there was some sensory loss to pain though not to touch. The pupils and palpebral fissures were equal. No deformity, tenderness or limitation of movement of the cervical spine was present. There was no weakness in the lower limbs; the knee-jerks were hyperactive and equal; the plantar reflexes were flexor in type. The tentative diagnosis made at this time was that of a localised lesion, most probably intermedullary, at the level of the fourth and fifth cervical segments.

On October 28, 1927, the patient was admitted to Professor Bramwell's ward at the Royal Infirmary, Edinburgh. Some days previously he had wakened in the middle of the night with pain in the back of the neck, but this disappeared after he made some movements. The weakness of the arms had become progressively worse till, when examined in hospital, the patient was quite unable to lift the left arm and, with the right arm, movement was possible only below the elbow. On both sides, but to a greater degree on the left side, the deltoid, biceps, brachoradialis, infraspinatus and supraspinatus were markedly atrophied. The dynamometer readings were: left hand, 90; right hand, 110. There was no incoordination or intention tremor and there were no fibrillary tremors of muscles. The wrist and triceps jerks were active and equal on the two sides, but the biceps-jerk was only just perceptible on the right side and absent on the left. The abdominal reflexes were active. The jaw-jerk was unusually active. Knee and ankle jerks were hyperactive, but there was no clonus. Plantar responses were flexor. Tenderness was elicited on pressure over the fourth cervical spine, but, in contrast to the sensory disturbance present eight days previously, no loss to pain could now be detected in the arms.

On November 1, 1927, the cerebrospinal fluid was examined for Wassermann's reaction and gave a negative result; the globulin was slightly increased in amount; cells were 2 per c.mm.; and the colloidal gold curve was 0012331100. X-ray photographs of the cervical region showed no abnormal appearances.

The patient remained in hospital until January 14, 1928. During the first part of this period /

period pain was occasionally present in the middle line at the level of the fifth and sixth cervical spines, but was controlled by pyramidon, 5 gr. Nearer the end of his stay in hospital, however, the pain was more constantly present and kept him awake at night. Treatment at first consisted of potassium iodide, 25 gr. t.i.d., and mercurial inunction; later, hypodermic injections of strychnine in increasing and decreasing doses were substituted. Some time after the course of injections had commenced the increased tendon reflexes in both legs became more exaggerated. Throughout the patient's stay in hospital the jaw-jerk was always elicited very easily. Before his discharge no additional muscles had become noticeably atrophied, and the weakness in those already affected had become only slightly more marked.

On February 14, 1928, the patient reported. He had suffered a considerable amount of pain in the neck, varying in intensity. The muscular weakness had gradually become more pronounced. Dynamometer readings were: left hand, 60; right hand, 85. There was now a definite extensor response on the left side, but the right plantar reflex was still flexor. The patient had never experienced any difficulty in walking.

On March 10, 1928, the patient again reported. In the interval the neck had become somewhat stiff, but the pain had not been so severe. The weakness in the hands had progressed and both arms were now practically powerless. Dynamometer readings were: left hand, 35; right hand, 60. When walking he experienced a stiffness of the legs and at times he tended to stagger. The plantar reflexes were the same as on the previous occasion.

On April 11, 1928, the patient was re-admitted to hospital. The weakness in the left hand had now advanced until it was absolutely powerless. Dynamometer readings were: left hand, 0; right hand, 50. Examination revealed over the limbs and trunk, from the fifth cervical distribution downwards, a general impairment of sensation to pain and temperature, but not to touch. Cerebrospinal fluid was withdrawn, simultaneously by cistern and lumbar punctures. The fluid from the lumbar route was xanthochromic and the pressure did not vary either on coughing or on compression of the jugular veins; that from the cisternal route was clear and, on both tests, showed a sharp rise in pressure. Examination /

Examination of the two fluids showed:-

Lumbar:- Cells = 17 per c.mm. Globulin markedly increased.

Cisternal:- Cells = 2 per c.mm. Globulin - a trace.

Following these punctures the patient experienced considerable pain in the neck and shoulders on both sides, and rapidly became paraplegic with incontinence of bladder and bowel.

The respective contents of the cerebro-spinal fluid from the two sources showed that a blockage existed within the spinal theca, somewhere between the cisternal and lumbar regions; from the other clinical data, the level of the lesion was undoubtedly in the neighbourhood of the fifth, sixth and seventh cervical segments.

Professor Wilkie was asked to see the patient with a view to operation, and it was decided to perform an exploratory laminectomy.

On April 19, 1928, the fourth to the seventh cervical spines and laminae were removed and the underlying dura mater exposed. The membrane looked and felt tense; the normal space between it and the posterior arch was obliterated, but the bony surfaces were not eroded. The third and seventh vertebral arches were then removed. The dura was incised in the mid-line about the level of the fourth cervical vertebra. There was a sudden gush of cerebro-spinal fluid under tension, but it was clear and not pigmented. The incision in the dura was extended to the extremities of the wound and, so far as could be seen, the vertebral canal was filled completely by a growth. The growth was examined above, below, and at the sides, but no point of separation of tumour from cord was found. The tumour consisted of a fusiform expansion of the substance of the cord. Removal therefore was out of the question, and 10 mg. of radium were laid in tubes on the surface (one tube of 5 mg. and five tubes of 1 mg.).

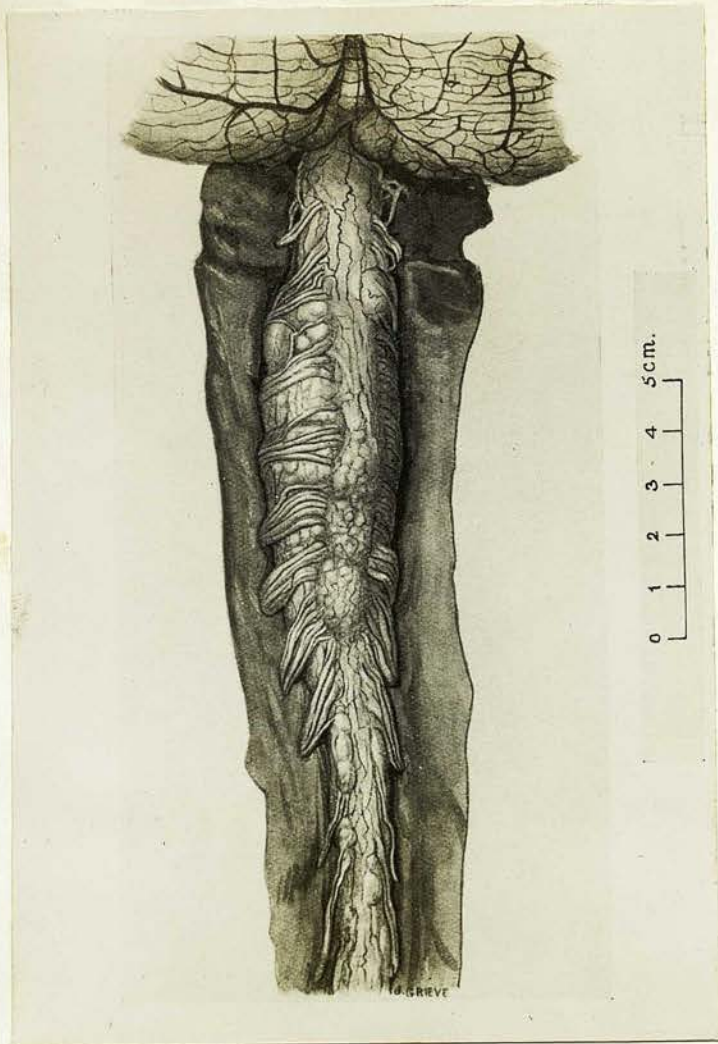


Fig. X. - Illustrates the fusiform expansion of the cord due to the glioma.

A few hours after the operation the patient died of shock.

Autopsy:- At autopsy the brain, spinal cord and spinal meninges were removed in one piece. The fusiform expansion of the substance of the cord was found to extend from about the third cervical to the first thoracic segment. Laterally, and also posteriorly, between the levels at which the nerve roots entered the cord, nodular swellings were present.* The whole tumour was surrounded by the pia-arachnoid membranes and at no place was it adherent to the dura mater. Away from the swelling, no abnormality of the spinal cord was observed.

After fixing in formol-ammonium-bromide for a few days, the cord was examined by making transverse incisions at various levels.

Two separate and small hæmorrhages were found, one on each side in the antero-lateral portions of the cord and extending from the sixth cervical to the first thoracic segments. The maximum area of that on the right side occurred in the seventh cervical segment. The hæmorrhage on the left side was smaller in transverse extent than was that on the right.

In sections taken transversely through the centre of the fusiform swelling, no differentiation into grey and white matter was seen. To the naked eye the medulla was not involved by the neoplasm, but subsequent microscopic examination showed that it had extended for some distance into this region.

Microscopic examination:-

1. A portion comprising the whole transverse diameter was taken from the centre of the fusiform swelling and was placed for twenty hours in Helly's modification of Zenker's fixative and thereafter carried through the routine procedure for paraffin sections. These were stained by Meyer's acid hæmatin and eosin.

2. Frozen sections of the tissue removed from /

* Fig. X.

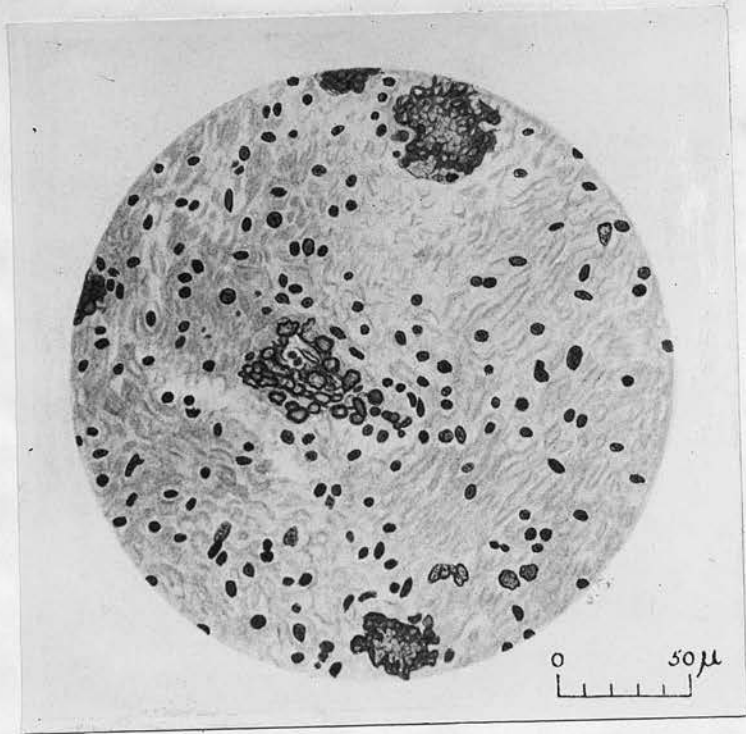


Fig. XII. - Paraffin section stained by hæmatoxylin and eosin. Small globular masses of calcareous material have been deposited in an area of the glioma undergoing necrotic changes. In the centre of the field the deposition is seen to have occurred around a small blood vessel.

from various levels were impregnated by Cajal's gold chloride sublimate method and by various silver methods.

Sections cut in paraffin and stained by hematin and eosin demonstrated that in the centre of the fusiform swelling the entire internal structure of the cord had disappeared, the whole tissue being a mass of protoplasm very rich in nuclei. As compared with the nuclei of the peripheral protoplasm, those in the central parts were small, deeply staining, and were losing their structure (pyknotic changes).

The nuclei of the peripherally situated protoplasm varied in size; the great majority of them were round or oval, large, and rich in chromatin. Some of the oval nuclei were of great size and contained a large amount of deeply staining chromatin.

In certain places the nuclei were grouped together, giving the appearance of a multi-nucleated or polymorpho-nucleated giant cell. In some instances, these groups of nuclei were of the extremely large type.*

The structure of the neoplasm, therefore, as demonstrated in paraffin sections, was typical of the "giant-celled glioma of Stroebe."

For the most part, the blood vessels in the neoplasm were not numerous and their walls not thickened. In a few instances the smaller vessels contained hyaline thrombi.

Numerous small rounded or oval masses of calcareous material were present in those portions in which the nuclei were undergoing pyknotic changes; the deposition had occurred in the form of small spherular bodies, and hence the whole mass had a crenated outline. In certain instances the small spherules were discrete and scattered over a rather larger area than that occupied by the aggregations. In other instances the deposition had occurred in the perivascular sheaths of small blood vessels.**

Transverse /

* Fig. XI. ** Fig. XII.

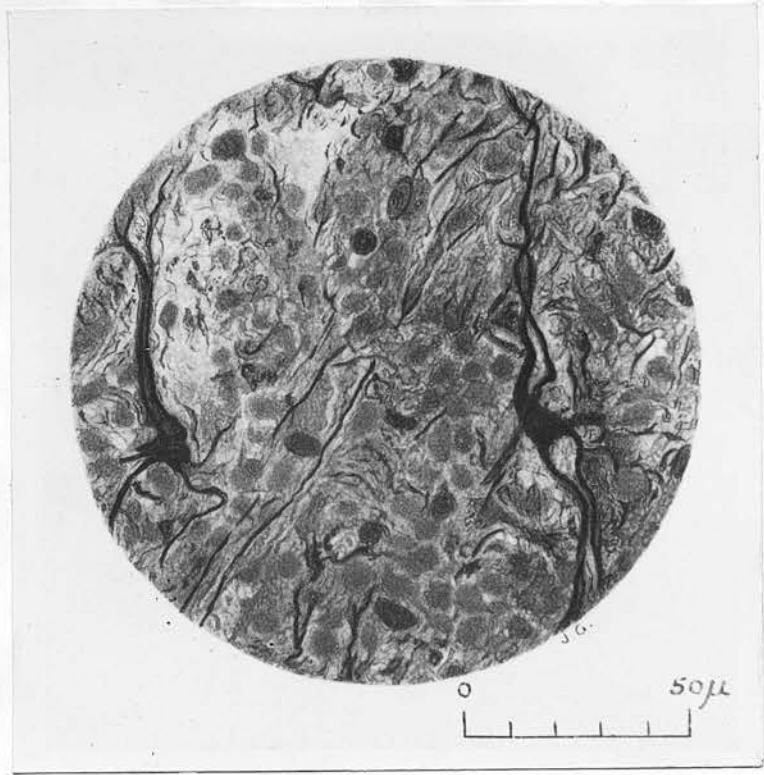


Fig. XIII. - Frozen section treated by Cajal's gold chloride sublimate method. Two of the pre-existing astrocytes involved by the glioma are in process of disintegration.

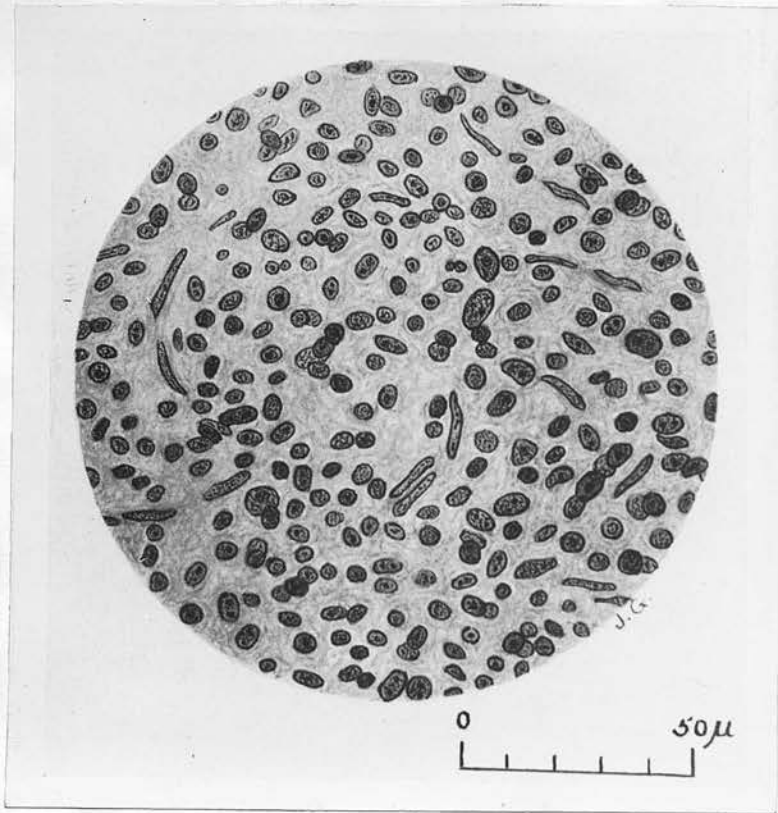


Fig. XIV. - Frozen section, treated by Hortega's silver carbonate method, demonstrates the syncytial character of the glioma. (The elongated nuclei are those of the endothelial cells of the blood vessels.)

Transverse sections taken from the centre of the fusiform swelling (cervical segment 6), treated by various silver impregnation methods and by Cajal's gold method, showed that for the most part the neuroglial septa had disappeared, small portions only remaining; no trace of the central canal was seen. A certain number of astrocytes in various stages of disintegration were still present; their bodies and processes were swollen and the latter were to a greater or lesser extent fragmented (clasmotodendrosis).*

The structure of the neoplasm was that of a syncytium: numerous large nuclei, varying greatly in size, were embedded in a protoplasmic matrix in which were no cell boundaries.**

Transverse sections taken through the lower part of the neoplasm (level of cervical 8 and thoracic 1) showed that the neoplastic growth in the cord was confined to the posterior columns; the membrana superficialis and the septa were intact, but the pia-arachnoid meshes dorsal to the posterior portion of the cord were distended and filled by the neoplasm. In these situations the structure of the neoplasm was of the same syncytial character as was found elsewhere. Serial sections cut in paraffin showed that the neoplasm had reached the pia-arachnoid spaces by infiltrating along the posterior roots.

A cyst some 2 mm. in diameter, due to liquefactive necrosis of neoplastic tissue was present in one of the posterior columns immediately behind the grey commissure. Its wall was composed of the pre-existing interstitial elements of the cord in which were islands of more or less necrotic neoplastic tissue; it contained fluid with a certain number of fragmented fibres and granular corpuscles.

Paraffin sections showed that certain portions of the tissue around the cyst were very vascular, numerous well-formed blood vessels being present, and in this area a segment of the wall consisted of very recently proliferated capillaries.

The astrocytes of the grey matter, but particularly those of its antero-lateral portion on both /

* Fig. XIII. ** Fig. XIV.

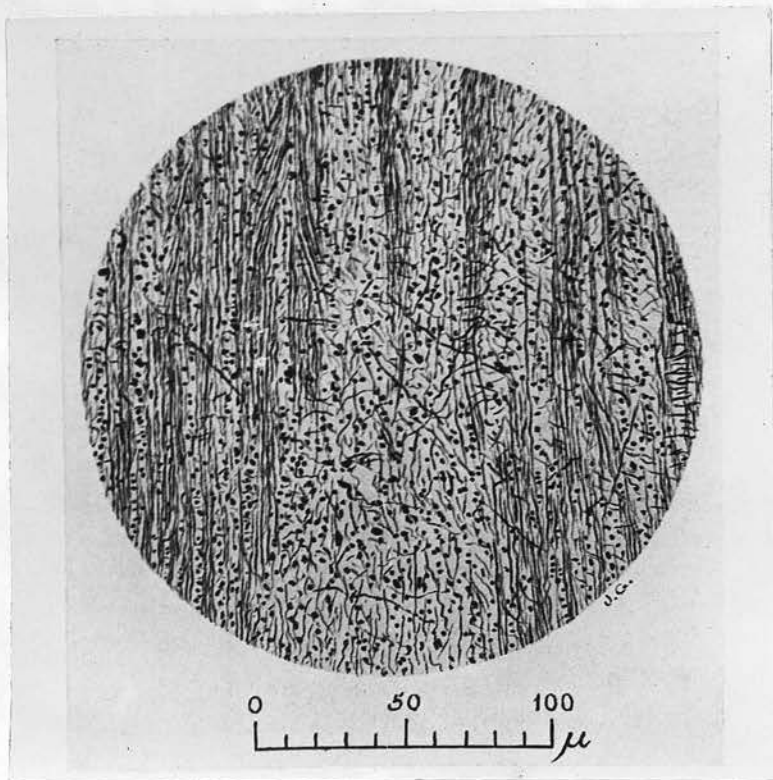


Fig. XV. - Longitudinal section from the upper part of the neoplasm treated by Gross-Bielschowsky method, shows the tumour extending in the form of infiltrating strands. The nerve fibres are atrophying and disappearing.

both sides, were undergoing very active amitotic proliferation; they were numerous, large, and deeply impregnated by gold; some of them contained two nuclei and many of them were closely approximated in pairs.

Longitudinal sections were made from a portion 2.5 cm. long, comprising the upper part of the spinal cord and lower part of the medulla. These sections showed that strands of the neoplasm had infiltrated upwards; at the lower levels some of the strands were of considerable size. In the medulla they were numerous but narrow, passing between and parallel to the nerve fibres.

Sections prepared by Gross-Bielschowsky's method demonstrated that where the neoplastic tissue was large in amount the majority of the nerve fibres had disappeared. Those which had persisted were greatly atrophied and some of them showed fragmentation*. Nodular swelling and the other forms of degeneration of nerve fibres found in experimental lesions (Cajal and others) were not observed.

Longitudinal sections of the lower part of the neoplasm and of the adjacent cord presented a similar picture to the above, the neoplasm extending in the form of wider and narrower strands. Proliferation of astrocytes was again marked, especially in the grey matter which had not been involved by the new growth.

From the above it will be observed that in no part of the neoplasm was there any differentiation of the syncytium into cell elements resembling spongioblasts or astrocytes.

Deductions from the Case.

1. Clinical Course:- The case presents several features of clinical interest. When first seen

the /

* Fig. XV.

the distribution of the progressive wasting and its symmetry, the pain which had been complained of about the spine of the left scapula, and the sensory impairment along the radial aspect of the upper limbs, pointed to a gross lesion at the level of the fourth, fifth, and sixth cervical segments of the spinal cord. The preponderance of the motor symptoms and the absence of evidence of interference with conduction in the spinal cord suggested that the lesion was situated anteriorly, although it was doubtful whether it lay in the substance or on the surface of the cord. Again, the X-ray examination showed no evidence of disease of the bone, while the negative result of Wassermann's reaction and the inefficacy of treatment with iodide and mercury appeared to justify the exclusion of a syphilitic lesion. Further, the examination of the cerebro-spinal fluid at this period /

period afforded no positive diagnostic evidence. The facts that after the patient's admission to hospital no sensory disturbances were detected, that the jaw-jerk was unusually active, and that the pain complained of had never been an obtrusive symptom, raised the question whether the case might be one of amyotrophic lateral sclerosis. The muscular wasting, however, was strikingly symmetrical and conformed with a nerve-root distribution; moreover, there were no fibrillary tremors.

At a later date the results of combined cistern and lumbar punctures, together with the onset of sensory disturbance with a spinal distribution corresponding to a particular level, afforded definite proof of the presence of a gross lesion not only interrupting the circulation of the cerebro-spinal fluid but also involving the cord in the mid-cervical /

mid-cervical region. The lesion was undoubtedly a neoplasm, but whether situated in the substance or on the surface of the cord was still doubtful, and this was only determined at the operation.

As demonstrated at autopsy, the relationships of the neoplasm showed that the pain complained of must have been due to pressure by the tumour upon the fourth and fifth posterior cervical roots.

Again, the paraplegia which developed so suddenly after the cistern and lumbar punctures was caused most probably by disturbance of pressure followed by hæmorrhage. It may be that the cerebro-spinal fluid above and below the tumour was exerting a protective influence by distending the theca, and that its removal resulted in rupture of two or more diseased blood-vessels.

2. Pathology:- It is commonly stated that a glioma rarely /

rarely, if ever, spreads from the substance of the brain or cord into the pia-arachnoid spaces, whereas an ependymoma of the brain-stem or cord frequently does so. It might be maintained, therefore, that the neoplasm in this case had arisen from the ependyma and not from the neuroglia. Such a differentiation is of no moment, however, since genetically both the ependyma and neuroglia are identical. At most, the so-called "ependymoma" can be considered only as a type of glioma.

The preparations treated by the gold and silver methods demonstrate the neoplasm to be a syncytial glioma throughout. The type of neuroglia of which the neoplasm is composed has its counterpart in the earliest form of developing neuroglia present in the neural tube, namely, the syncytium described first by His. The only histological difference between /

between the elements of the neoplasm and of the normal syncytium of the neural tube in its earliest stages is in the increased number and varied size of the neoplastic nuclei and in their large chromatin content.

Had the patient survived longer, it is conceivable that the neoplastic syncytium would have become differentiated into individual neuroglial cell elements, having as their prototypes normal spongioblasts or even astrocytes. It seems probable to me, however, that such differentiation would not have occurred, since it is justifiable to presume that the neoplasm would have continued to extend, but that the relative phases present at the time of death would have been maintained, namely, a progressive zone of newly-formed living neoplasm surrounding a core in which necrotic changes were simultaneously /

simultaneously advancing.

In the present case the necrobiotic changes in the central portions of the neoplasm might be explained by the increasing pressure of the growth against the dura mater and surrounding bony canal gradually diminishing the vascular supply and so leading to inadequate nourishment. In general, however, necrosis occurring in neoplasms can be explained only to a certain extent by insufficient blood-supply; some other factor, at present undefined, must come into play.

So far as I am aware, no neoplasm having a structure typical of the "large-celled glioma of Stroebe" has been investigated hitherto by gold and silver impregnation methods. In the present case the latter methods have shown that the structure associated with the "large-celled glioma" is that of a /

a syncytium.

The deposition of the calcareous material in the present case requires consideration. Deposition of calcareous salts in dead material is a frequent occurrence and, speaking generally, it is quite commonly met with in the portions of neoplasms which have undergone necrosis. Although necrosis occurs almost invariably in parts of gliomata, it is exceedingly rare to find calcareous deposition taking place within it. Why this is so is difficult to explain; calcareous deposition in necrotic tissue is intimately related to fatty material deposited in the process of disintegration. In areas of necrosis in the central nervous tissues, lipoids and other bodies of a fatty nature are found in large amounts, and it might be expected therefore that the brain and cord would be a frequent site of calcareous /

calcareous deposition in conditions in which disintegration of their tissue takes place. Although the large amount of fatty bodies resulting from the disintegration of elements of the cord may explain the deposition of the lime salts in the present case, it seems to shed no light as to why similar deposition does not occur frequently in gliomata.

The last point to discuss in the pathology of this case is the proliferation of the astrocytes adjacent to the neoplasm.

It has been noted that both at the upper and at the lower ends, where the neoplasm was not occupying the whole area of the cord but was extending in the form of narrow infiltrating processes, the astrocytes in the neighbourhood were undergoing active proliferative changes.

In the majority of those gliomata in which /

which the neoplastic cells become differentiated to the degree of forming astrocytes, it is this change at or near the growing portions which gives rise to difficulty in deciding, firstly, whether the proliferating astrocytes are neoplastic or pre-existing, belonging to the "normal" tissue of the cord, and secondly, whether the change is one affecting the pre-existing astrocytes, causing them to become neoplastic under the influence, as it were, of the neighbouring new growth.

In the present case there can be no possible confusion between the neoplastic tissue and that pre-existing, since the structure of the former is syncytial throughout its whole extent. Moreover, the complete differentiation and histological perfection of the proliferating astrocytes in this case make it certain that the changes are those of proliferation /

proliferation and not a metamorphosis into a neoplastic state.

Further, proliferative changes in the connective tissue in the neighbourhood of a neoplasm occur in many infiltrating new growths other than gliomata. The question as to whether the proliferative changes in the neighbouring stroma are to be interpreted as a neoplastic change does not arise in these cases, since the tumour cells and the stroma cells are of an entirely different structural character, e.g., epithelial and connective tissue.

Various interpretations have been given to the significance of the proliferative changes in the stroma. One of the commonest put forward is that they are an expression of a defensive mechanism; in other words, that it is an attempt on the part of the body to form a barrier to the invasion of the neoplasm /

neoplasm.

That wherever damage and destruction of tissue occurs, proliferative changes take place in those cells which have retained the potentiality to divide, is a law of general application. This is seen, for example, in the case of a wound in any part of the body and in inflammatory processes wherever they occur. It is outside the present purpose to discuss the nature of the stimulus to this reaction, but it might be suggested that probably it is associated with the products of autolysis of the dying tissue elements and that the reaction is the result of phylogenetic development, since it is the fundamental process underlying healing and repair.

In the case of an invading neoplasm, tissue is destroyed and, according to the general law enunciated above, the neighbouring cells, capable of proliferating /

proliferating, will pass into an active vegetative phase and begin to divide. Moreover, if the stimulus to proliferate be in whole or in part what is suggested, the lytic products may be reinforced by products derived from the metabolism of the neoplastic cells. It is known that these differ from the products of the "normal" cells and, being "abnormal", they may act on the neighbouring cells, stimulating them to reproduce just as do the products of lysis.

3. Gliomata of the Cord in General:- The great majority of cases published under the title of tumours of the cord refer to neoplasms arising not from the cord, but in association with its membranes.

The only neoplasms which can arise from elements of the spinal cord are: (a) gliomata (including ependymomata); and (b) those in which the /

the specific cells have as their prototype the nervous parenchyma (neurocytomata).

In a series of 187 cases collected by Ewing²⁶ of neoplasms occurring within the bony canal of the spine, only 45 (24 per cent.) were actually neoplasms of the cord.

Statistics, quoted by Elsberg²⁷ from different sources and collected by various authors, give the number of intramedullary as compared with extramedullary neoplasms of the cord as between 20 and 28 per cent. In his own cases, out of 100, only 14 were found to be intramedullary. A further analysis of these 14 cases showed that 8 (57 per cent.) occurred in the cervical and 6 (43 per cent.) in the thoracic portion. But it should be remembered that Elsberg's figures are taken from the statistics of a surgical clinique.

Schlesinger's statistics²⁸ show that whereas in the dorsal region meningeal neoplasms are four times as frequent as medullary growths, in the enlargements the latter tend to predominate.

Many authorities look upon the neuroglial hyperplasia, which is the essential change in syringomyelia, as being of the nature of a neoplasm (glioma) extending for a shorter or longer distance in the cord. It would seem more likely that the essential difference between hyperplasia of the neuroglia (gliosis), such as occurs in syringomyelia and neoplastic growth (glioma), is that in the former, although reproduction of the neuroglial elements occurs, the growth is restrained, whereas in neoplastic proliferation the growth is uncontrolled.

The pathology of this case of a cerebral glioma follows in natural sequence to the previous one. Moreover, the investigation has helped to confirm my views as to the unscientific basis of certain classifications of gliomata which have been advanced in recent years - views which have been impressed upon me by the investigation of all the present series of cases.

J.D., male, aged 46, a Mining Inspector, was admitted to the Royal Infirmary on February 3, 1928, complaining of severe frontal headache, drowsiness and vomiting. The patient had enjoyed excellent health up to a week before admission to hospital when symptoms had commenced suddenly.

On examination the patient was apathetic but he was not aphasic. Papilloedema was marked in both eyes. There was no muscular weakness or in-co-ordination. The reflexes were brisk and equal and Wassermann's reaction on the blood gave a negative result.

Some days later the patient developed a left sided paresis; he gradually passed into a coma and, a hypostatic pneumonia supervening, died on February 23, 1928, some four weeks after the onset of symptoms.

Autopsy:- The cerebral convulsions on both sides were found to be markedly flat.

After removing the brain a medial sagittal section showed the body and knee of the corpus callosum to be involved by a neoplasm, but the splenium had /

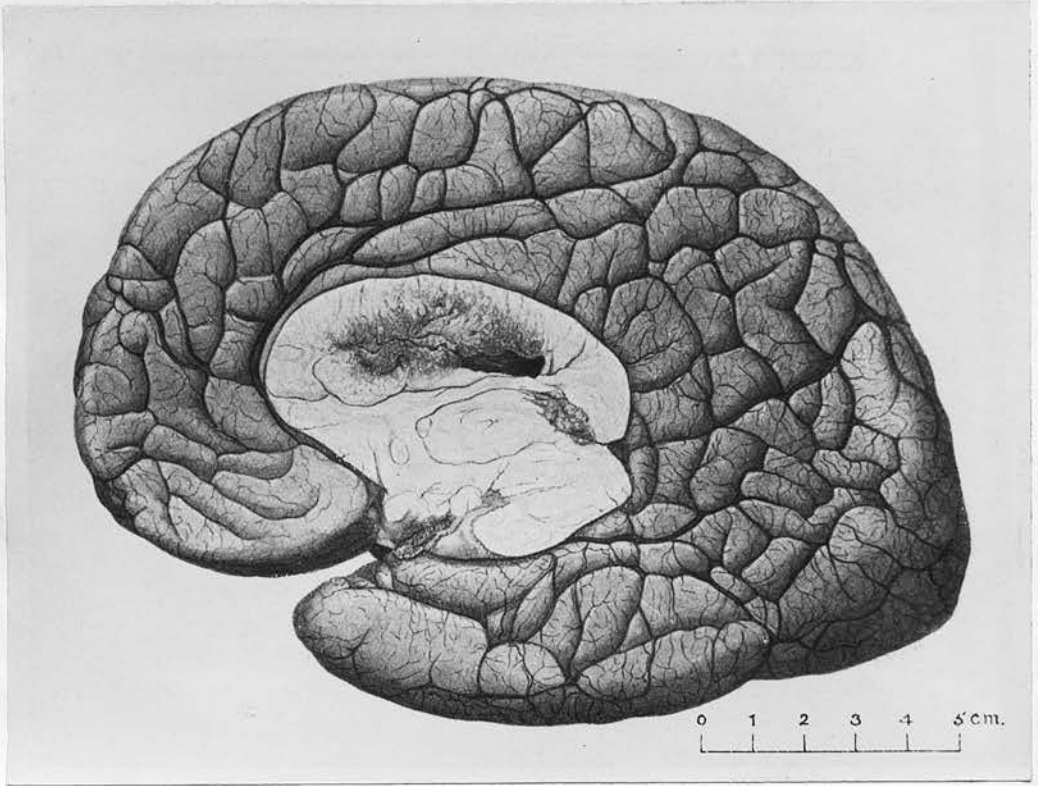


Fig. XVI. - Medial sagittal section showing involvement of the body and knee of the corpus callosum by the glioma.

had not been invaded. The portion of the neoplasm situated in the corpus callosum was pinkish in colour with dark areas of necrosis.*

Sagittal sections were made through each hemisphere. On the right side the neoplasm which was rather paler in colour than the cerebral tissue extended diffusely both in an anterior, posterior and in a lateral direction, involving a considerable portion of the white matter, but its limits were not well defined to the naked eye, the obviously neoplastic tissue merging into that which appeared normal. A hæmorrhage rather more than 1 cm. in diameter was situated in the subcortical white matter in the neighbourhood of the precentral gyrus, 1.5 cms. below the surface. The extravasated blood was dark red in colour and the clot was very loosely held together. The tissue lying deep to the hæmorrhage was considered to be neoplastic but that superficial showed no macroscopic change from the normal. (Later microscopic examination revealed however that neoplastic tissue was present superficial to the hæmorrhage and had invaded the cerebral cortex).

On the left side the neoplasm had invaded the white matter of the hemisphere in a similar manner, but as far as could be seen it was not so extensive as from the right side.

Microscopical Examination:- Portions of tissue were taken from each side, about 2 cms. from the middle line and, having been divided into pieces of suitable size, were fixed in Helly's modification of Zenker's solution. Thereafter the pieces were carried through the routine procedure for paraffin section and were stained by Mayer's acid hæmatin and eosin and by Heidenhain's Azan method.

Pieces of tissue were taken from various portions of the neoplasm, including those near the corpus callosum and those near the periphery in the neighbourhood of the subcortical hæmorrhage, and were fixed in formol-ammonium bromide solution. Frozen sections made from these were treated by Cajal's gold chloride sublimate, by Hortega's silver carbonate and other silver impregnation methods, and by /

* Fig. XVI.

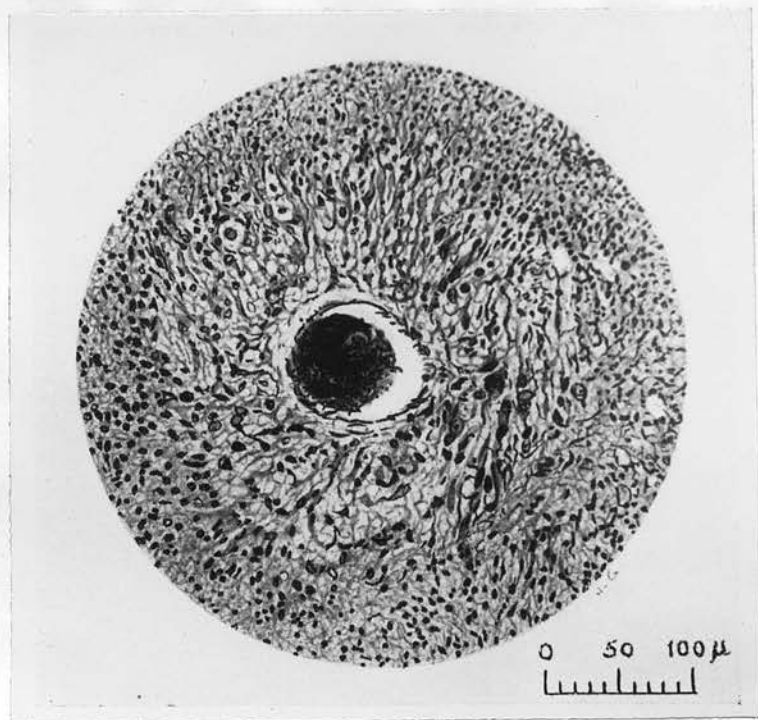


Fig. XVII.-- From a necrosing portion of the glioma. The neoplastic tissue immediately around the central blood vessel is still living, whereas that more distant is necrosed. The phenomenon is that of the so-called pseudo-rosette.

(Frozen section treated by Hortega's silver carbonate method).

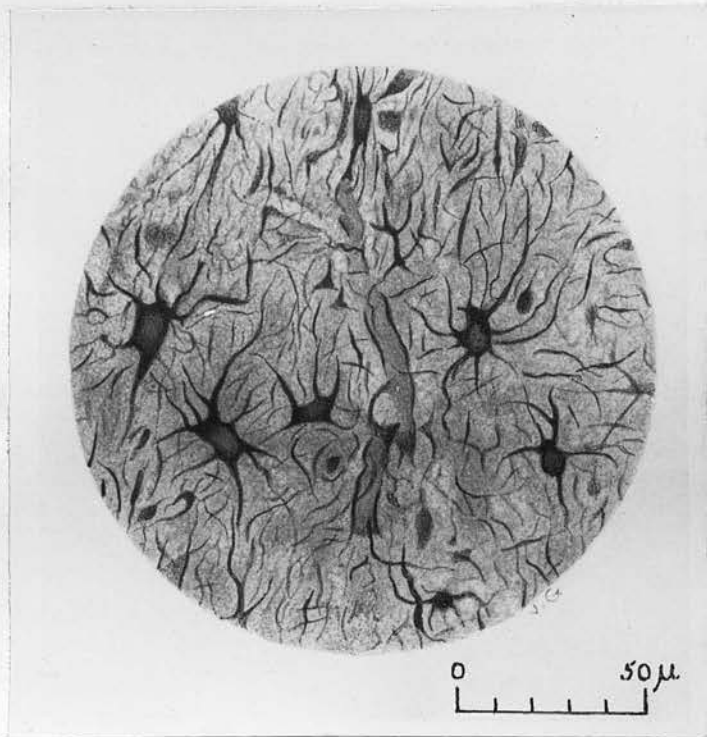


Fig. XVIII. - From the neighbourhood of the corpus callosum. The neoplastic astrocytes are large and numerous, and have reached a high degree of differentiation.

(Frozen section treated by Cajal's gold chloride sublimate method).

by Morgan's method for demonstrating myelin sheaths.

1. Section of the more central part cut in paraffin and stained by hematin and eosin and by the Azan method showed the neoplasm to be a glioma rich in nuclei. The nuclei varied in size, the average being considerably larger than that of the normal astrocyte and they contained a large amount of chromatin.

Throughout the sections were many areas of necrosis; these areas consisted of a central mass of granular and structureless material surrounded by a zone in which the neoplastic nuclei were pyknotic and in various stages of disintegration. This appearance, therefore, was that frequently referred to by authors as the "palisade arrangement".

In many instances the neoplastic cells immediately around blood vessels were not necrosed, but the tissue situated more distal had disintegrated. Thus the picture presented in these portions was that of the so-called "pseudo-rosette".*

The walls of most of the arterioles were thickened, the thickening being chiefly in the inner zone although considerable fibrosis was present in the muscular zone. In many cases thrombosis of smaller blood vessels had occurred, and in some of these the thrombus had been organised into hyaline fibrous tissue.

2. (a) Section taken from the neighbourhood of the corpus callosum and treated by Cajal's gold chloride method demonstrated this portion of the glioma to be composed of numerous large astrocytes which had reached a high degree of differentiation. Many of their processes were long and thick and some of them were seen to come into relationship with blood vessels, but vascular foot-plates were not well formed. Occasionally a fibre had developed in one of the processes, but for the most part the neoplastic astrocytes were of the protoplasmic type.**

At some distance from the main mass of the portion /

* Fig. XVII. ** Fig. XVIII.

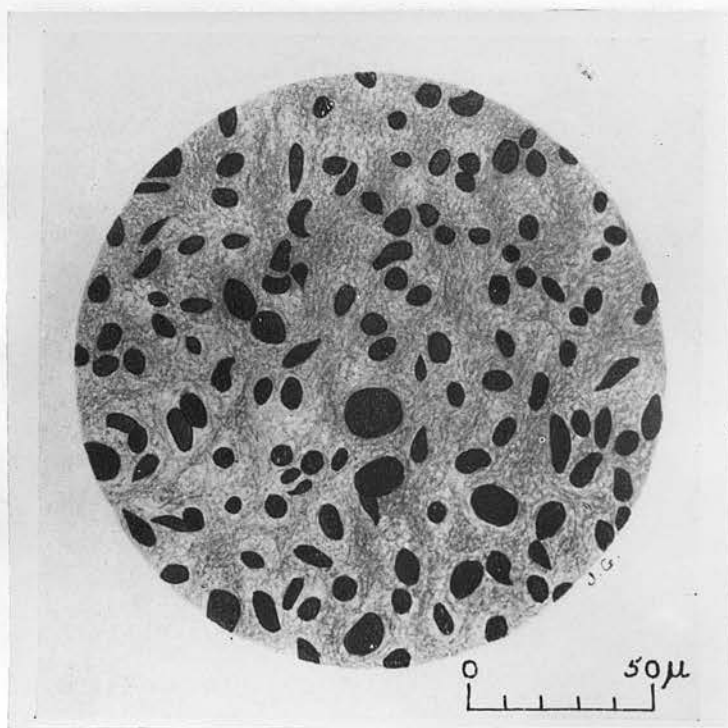


Fig. XX. - From the peripheral portion of the glioma. The structure is that of a syncytium, numerous large nuclei being embedded in a protoplasmic matrix.

(Frozen section treated by Hortega's silver carbonate method.)

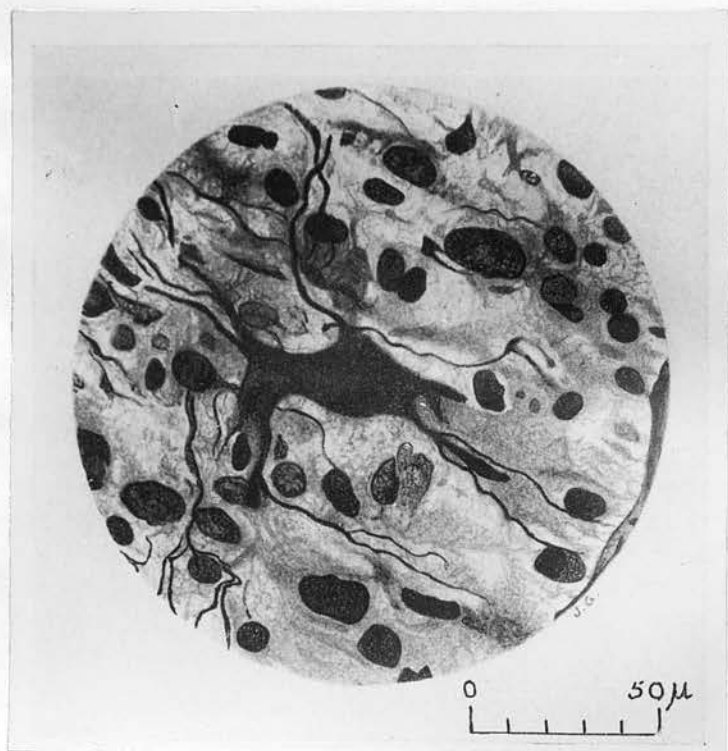


Fig. XXI. - From the peripheral portion of the glioma. The processes of pre-existing astrocytes involved by the actively growing neoplasm are swollen and disintegrating ("clasmato dendrosis".)

(Frozen section treated by Cajal's gold chloride sublimate method.)

portion of the glioma, involving the corpus callosum, small groups of fibrous astrocytes were seen which were large and with thickened processes but which showed structural perfection. Some of them contained two nuclei, being in a state of amitotic division.

At the periphery of the necrotic areas the neoplastic astrocytes were swollen and their processes were fragmenting. (Clasmatodendrosis).

(b) Section taken from the peripheral portions of the glioma, treated by Cajal's gold chloride and by Hortega's silver carbonate method, demonstrated that differentiation of the neoplastic cells was not nearly so advanced as in the central portion. The nuclei were numerous and showed great variation in size, some of them being exceedingly large.

In certain areas some of the neoplastic cells were elongated resembling the spongioblast of the developing central nervous system.* In other areas the structure was that of a syncytium, numerous large nuclei being embedded in a protoplasmic matrix.**

The pre-existing astrocytes involved by these actively growing portions of the neoplasm were undergoing clasmatodendrosis.***

3. Section of the peripheral portion of the neoplasm made by Morgan's method, showed that the myelin sheaths had disappeared in the neoplastic area. At the extreme periphery of the neoplasm a certain number of them persisted, but they were irregular in outline and the myelin had disintegrated into droplets.

4. Section of the peripheral portion of the neoplasm made by Gross-Bielschowsky's method, showed nerve fibres persisting in the neoplasm for a considerable distance below the costal layers and a certain number of them were present in these portions of the neoplasm which were necrotic. In these areas many of the nerve fibres present showed nodular swellings /

* Fig. XIX. ** Fig. XX. *** Fig. XXI.

swellings and were disintegrating into granules.

Discussion of the case.

Many of the pathological problems raised by this case have been discussed in the previous one. To avoid needless repetition these points will be referred to only so far as they require amplification in view of the differences in the histological structure of portions of the glioma which forms the subject of the present case.

From the comparatively large amount of necrosis present and the high degree of specialisation reached by the neoplastic astrocytes, there is no doubt that the portion of the glioma in and around the corpus callosum was of older standing than the peripheral portion. Further, whereas the cells in the older part had passed into a quiescent phase the elements in the peripheral portion were in a very active /

active vegetative condition.

The glioma had arisen therefore in the central portion of the brain and had extended widely in both cerebral hemispheres. The structure of the actively growing peripheral portions was largely that of a syncytium, and the only differentiation of the elements near the periphery was into cells, having as their prototype the spongioblast of the developing central nervous system.

Hence the gliomatous elements showed all degrees of structural differentiation from the syncytium to cells having a very close resemblance to the fully developed normal astrocyte.

The demonstration of the manner of growth of the glioma is the special feature of this case and is a syncytial infiltration of the surrounding cerebral tissue which explains the difficulty experienced in differentiating /

differentiating by the naked eye between the normal cerebral tissue and the adjacent neoplastic glia.

It is probable that many gliomata grow as a syncytium. Veszpremi²⁹ maintained that in the majority of cases the glioma has a syncytial character in its actively growing peripheral parts, whereas in the older central portion the element has differentiated into individual isolated cells.

Under the microscopic examination of the present case it was noted that at some distance from the neoplastic tissue small groups of enlarged fibrous astrocytes were present and that some of them were even in a stage of division. That these astrocytes were pre-existing cells and not those of an invading process of the glioma which had been cut transversally, was concluded not so much from their position in relation to the neoplasm as from the structural perfection /

perfection which they represented.

The significance and explanation of groups of astrocytes similar to those described has been discussed in the previous case.

The present case well illustrates the necrosis which is so common a feature in gliomata. Death of the cells is due, probably, to a number of factors. Of these, an insufficient nourishment of the cells is present in most instances and results firstly from the rapid proliferation of the neoplastic cells, causing the tumour to outgrow the blood supply and secondly, as demonstrated in this case, to thrombosis of blood vessels in the neoplasm. On general principles these thromboses occur owing to injury of the endothelium lining the lumen of the blood vessel, and hence the question arises as to the nature of the agent which causes the damage.

It /

It is an anatomical fact that every astrocyte, normal or neoplastic, has at least one or probably more of its processes which come into relationship with the perivascular adventitial lymph sheath of the blood vessel and which enters into the formation of the membrana limitans perivascularis. In my opinion, as a result of this anatomical relationship in the case of the astrocyte, absorption and excretion of metabolic substances occur through these processes. During rapid reproduction of these cells not only are metabolic products excreted into the perivascular lymph clefts in much larger amounts than under normal conditions but in the case of neoplastic cells it is known that the chemical nature of their effete products differs from those of the normal cells. It is justifiable to presume that the mechanism by which the waste products are drained away whilst sufficient /

sufficient for more ordinary conditions, cannot cope with the great excess of excretion. Consequently the fluid in the perivascular lymph spaces becomes saturated with the waste product, and I suggest that it is their presence together, possibly, with their altered chemical nature, which is responsible for the damage to the vascular endothelium.

In the present instance, therefore, it is seen that all stages of structural development are present from the simplest, namely the syncytium, to the most complex, the astrocyte, and this fact would suggest that it might be better to interpret the structure of the gliomata along lines of progressive specialisation of their elements rather than to attempt to allocate them to a particular structural category.

From the point of view of determining and interpreting /

interpreting the structure of a glioma, the present case illustrates the necessity, firstly, of placing material of suitable size into fixatives as soon as possible after death so that it may be examined adequately by gold and silver impregnation methods, and, secondly, of examining different portions of the glioma.

Deductions from the Case.

1. The present study is of a glioma cerebri which began in the central portion of the brain and extended widely into both cerebral hemispheres.

2. The older parts of the neoplasm consisted of astrocytes which had attained a high degree of specialisation, whereas the actively extending and recently formed portions were composed of a syncytium and of cells having as their prototype the /

the spongioblast of the developing neural tube.

3. At some distance from the neoplastic tissue there were small groups of pre-existing astrocytes which were proliferating.

4. Necrosis in the neoplasm was due probably in part to its outgrowing the blood supply and to the accumulation in the tissue of the waste products of neoplastic metabolism.

5. It is suggested that it is better to interpret the structure of gliomata along lines of progressive specialisation of their elements than to allocate them to a particular structural category.

These two cases which have now been considered in great detail showed from a structural standpoint a great contrast. In the glioma of the spinal /

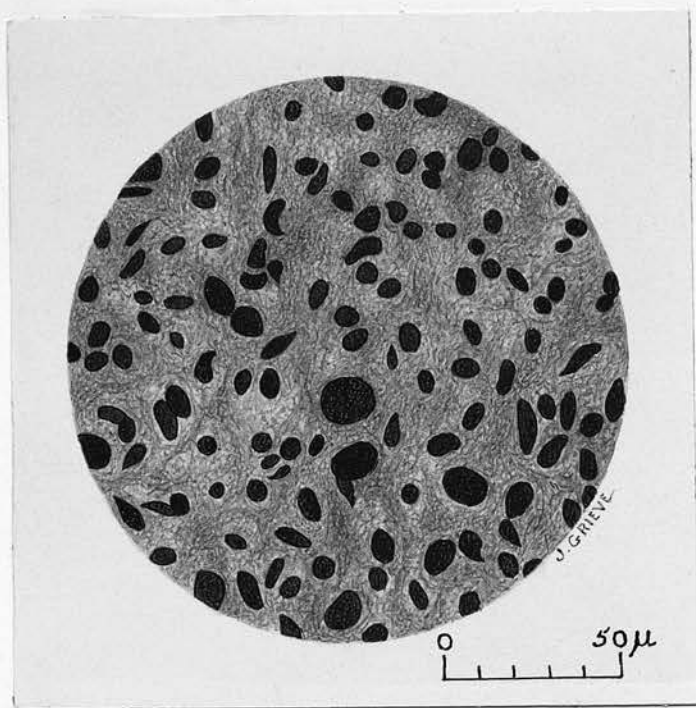


Fig. XXII. - From the periphery of a glioma. The structure is that of a syncytium; no individual cells have differentiated out. The neoplastic nuclei are large and numerous.

(Frozen section impregnated by Hortega's silver Carbonate Method).

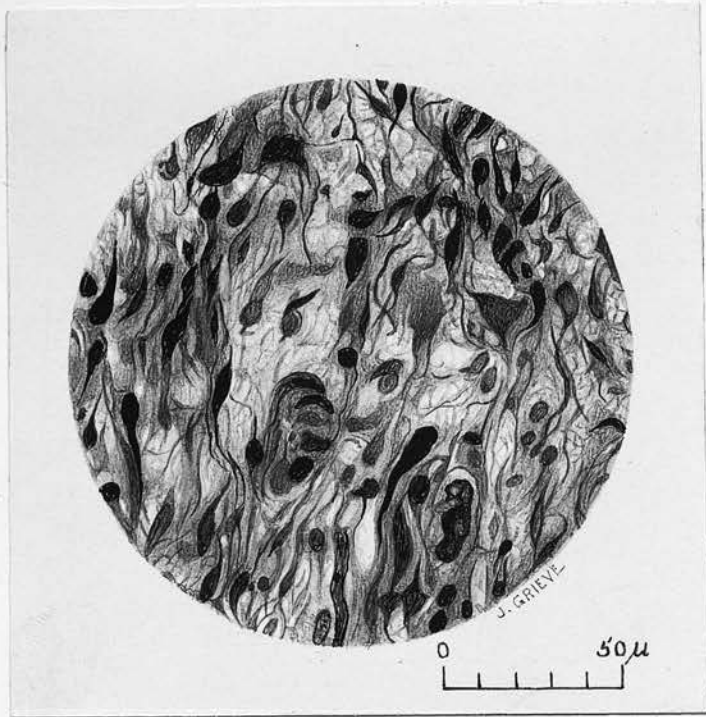


Fig. XXIII. - Near the margin of the same glioma (Fig. XXII.). Cells have differentiated out; they are elongated and resemble the spongioblasts of the developing neural tube.

(Frozen section impregnated by Hortega's Silver Carbonate Method.)

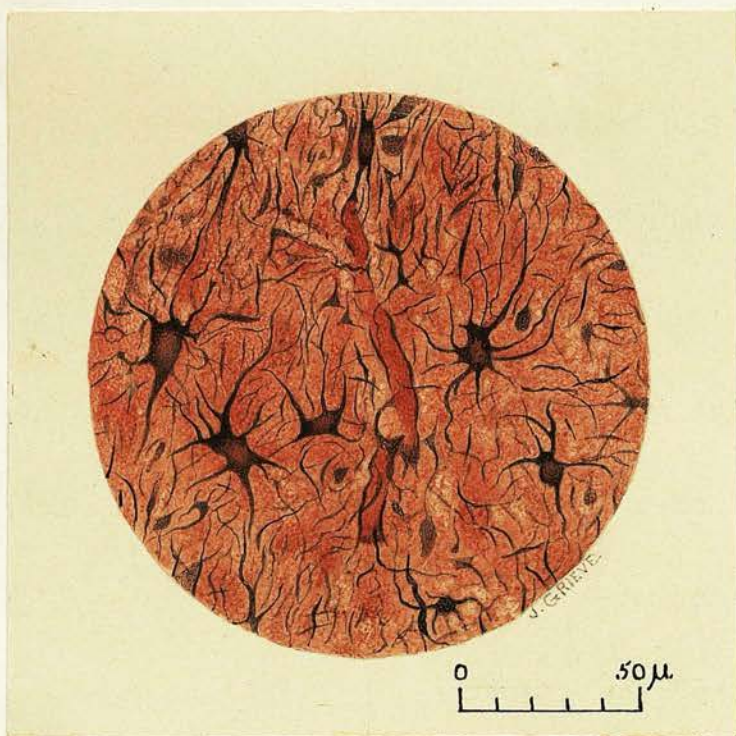


Fig. XXIV. - From the central older portion of the same glioma as in Figs. XXII. and XXIII. The neoplastic astrocytes are large and numerous and have reached a high degree of structural perfection.

(Frozen section impregnated by Cajal's Gold Chlorate Sublimate Method.)

spinal cord, it was demonstrated that the tumour consisted of a syncytium; nowhere had differentiation into individual cells taken place. In the case of the large glioma of the brain, it was shown that, whereas the growing portion and newly formed parts consisted of a syncytium* and of cells which had as their prototype the spongioblasts of the developing neural tube;† the older parts of the neoplasm consisted of astrocytes which had reached a high degree of structural differentiation.***

The interpretation of the latter case in which all stages of structural differentiation from the simplest form of neuroglia, namely a syncytium, to the most highly developed form, namely the astrocyte, was obviously to be made along the lines of progressive specialisation, an observation which is of great importance when one considers the tendency of the /

* Fig. XII. ** Fig. XVIII. *** Fig. XXIV.

the neuro-surgeon to classify these neoplasms according to the histological structure of a small portion obtained at operation.

H. S. Steenstand³⁰ in 1906 and R. Stumpf³¹ in 1911 described a syncytial part of the glioma and, as has been mentioned previously, Veszpremi in 1913 demonstrated that this structure is to be found especially in the peripheral parts of the tumour.

The cases in this series which have already been described focussed attention so strongly on certain features that it was decided to study the following important pathological points in all the cases under review:-

1. The manner in which gliomata grow.
2. The reaction in the surrounding tissue.
3. The occurrence of necrosis.
4. The occurrence of hæmorrhage.

All of these characteristics concern the general pathology of gliomata.

1. The /



Fig. XXV. - In the neighbourhood of the syncytial margin of a glioma. Cells have differentiated out and some of them have differentiated to a stage at which they can be recognised as astrocytes although they are yet far from mature. Part of the syncytium remains and is shown by the weakly impregnated nuclei around which no cell body has differentiated.

(Frozen section impregnated by Cajal's Gold Chlorate Sublimate Method.)

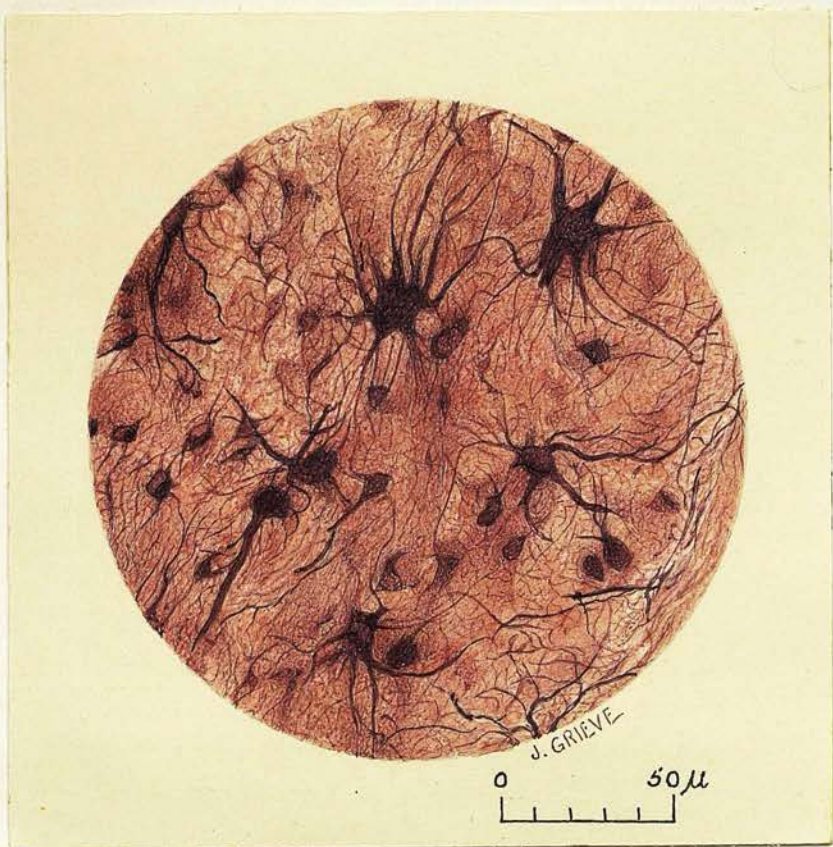


Fig. XXVI. - This part of a glioma was taken in the neighbourhood of the syncytial margin. Astrocytes have differentiated out; they are seen to have reached a high degree of structural perfection. Some of the syncytium still persists.

(Frozen section impregnated by
Cajal's Gold Chlorate Sublimite
Method.)



Fig. XXVII. - From the syncytial margin of a glioma. The neoplastic nuclei are large and numerous; many show karyorrhexis.

(Paraffin section stained by haematin and eosin).

1. The Mode of Growth of Gliomata:- In the large majority of cases the periphery of the neoplasm consisted either of a pure syncytium or of a syncytium out of which individual cell elements had differentiated. In none of these cases had differentiation reached the stage in which the astrocytes showed a high degree of structural development. On the contrary, the astrocytes were almost invariably undeveloped and possessed only a few short processes. Moreover, not only were many of these cells of the spongioblast type, but much of the protoplasm had not differentiated into individual cell units.* In most of these cases the gliomata appeared to have grown as a syncytium. In the syncytial portions the nuclei were very numerous and although they were of different size they were all very large and hyper-chromatic; many of them showed karyorrhexis. **

It /

* Figs. XXV & XXVI. ** Fig. XXVII.

It may be remarked here that not only was the structure of the neoplastic nuclei typical of nuclei in a proliferative phase but also other signs of growth were present. The previously existing astrocytes of the brain tissue were seen in the peripheral zone of the syncytium, and these showed great degenerative change; moreover, necrobiotic changes were present in the astrocytes of the neighbourhood which had not yet been invaded by the neoplasm but which were still outside the margin of the gliomatous syncytium. In those parts in which these appearances were present, there could be no doubt that the neoplasm was in a phase of active growth.

It is easy to understand how these gliomata growing as a syncytium spread by infiltrating the surrounding tissues, and why in consequence, it is often difficult or impossible on examination by the /

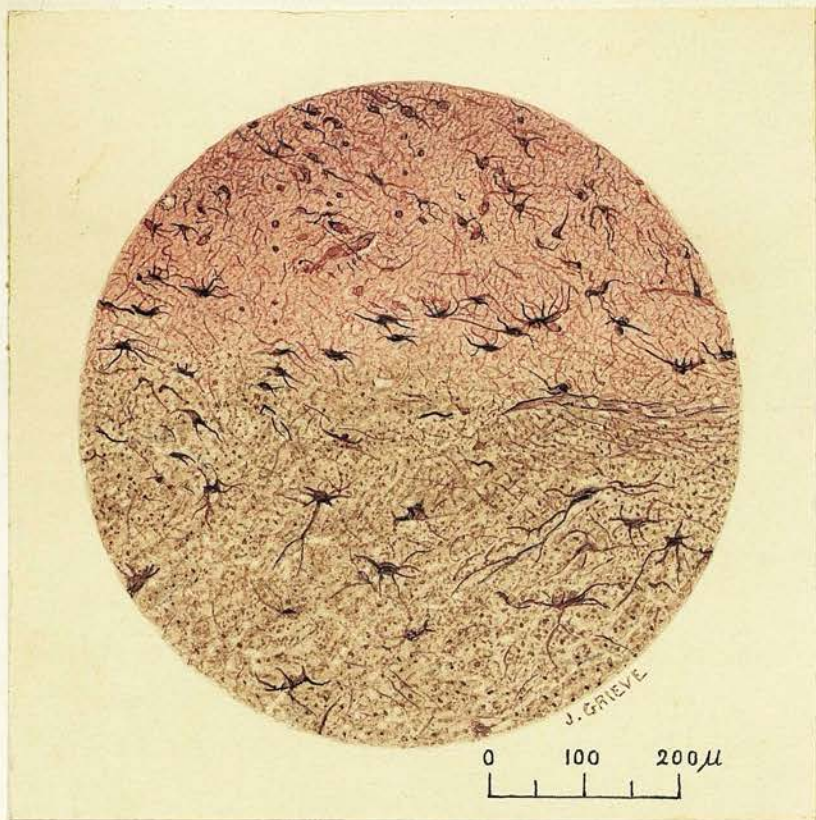


Fig. XXVIII. - The lower portion of the field consists of the syncytial portion of a glioma and in the upper part is cerebral tissue which has not yet been invaded by the tumour. The field illustrates both methods of growth - that by infiltration and that by pressure; the margin is fairly sharply demarkated; the proliferated (non-neoplastic) astrocytes at the margin of the tumour are elongated and their long axis are parallel to the margin (growth by pressure). On the other side certain astrocytes have been included by the infiltrating tumour (growth by infiltration) and show various stages of degeneration. The astrocytes near the neoplastic margin not yet included by the tumour show necrobiotic changes.

(Frozen section impregnated by Cajal's Gold Chlorate Sublimate Method).

the naked eye to find a sharp boundary between the neoplasm and the surrounding tissue; whereas infiltration is a frequent mode by which the glioma increases, microscopical examination of this series has shown that in certain cases, or at any rate, in certain parts of some of the gliomata investigated, the syncytial margin is sharply differentiated from the surrounding brain tissue; further, that the surrounding brain tissue is compressed and the astrocytes in it have assumed an elongated form, their long diameter being parallel to the margin of the neoplasm.* These appearances are brought about owing to the glioma growing by pressure. Hugo Ribbert³² recognised this method of growth and recorded that increase in size by pressure was the method adopted by these gliomata in which a sharp demarkation could be seen by the naked eye between the neoplastic and the surrounding /

* Fig. XXVIII.

surrounding tissue.

There were two cases found in which the peripheral zone was not syncytial. Although in both cases fibre formation was a marked feature, they differed from each other in many characteristics.

In the first case the neoplasm made itself manifest three weeks before death. At autopsy the tumour was found to have involved a large part of the left cerebral hemisphere and to have passed through the rostrum of the corpus callosum into the right cerebral hemisphere. Necrosis with the formation of cysts was a pronounced feature and small hæmorrhages were numerous; further it was seen that the neoplasm was somewhat fibrous.

Microscopical examination of portions of the peripheral zone demonstrated no syncytium; these parts consisted of astrocytes and large fibres. The astrocytes /

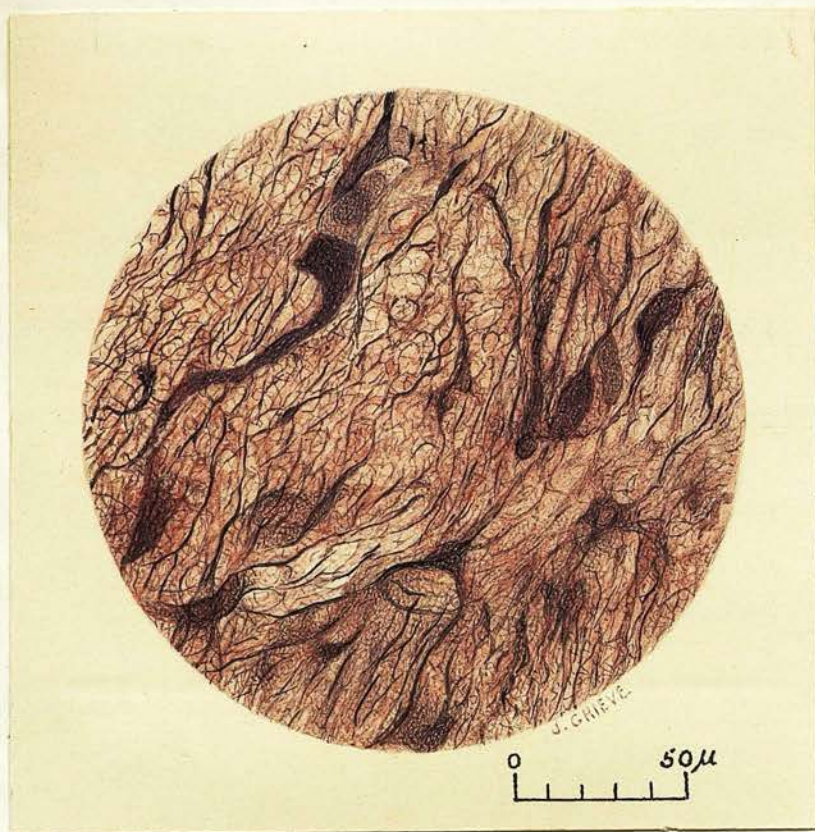


Fig. XXIX. - The portion of a glioma taken near its margin. The tumour consists of large immature astrocytes with thick processes and coarse fibres. Although this tumour can be classified as belonging to the "fibrous" type of glioma it is clear that it is very different from that figured in Fig. XXX.

(Frozen section impregnated by Cajal's Gold Chlorate Sublimate Method.)

astrocytes were immature and large, their processes were thick and some of them were of great length*. Many astrocytes had two or even more nuclei. In the central parts, the tissue showed much necrosis; in the living parts the astrocytes were more mature and the fibres, although still large, were of much less diameter than in the peripheral parts.

The astrocytes in the brain tissue surrounding the tumour had undergone great proliferation. This feature made it impossible to say with certainty whether single astrocytes at the margin belonged to the tumour or not. Well without the neoplastic zone amitosis of the previously existing astrocytes was demonstrated. Certain appearances in the neoplastic cells seemed to suggest that they were undergoing a similar process of division. The neoplastic cells, however, were so numerous that they appeared often in groups /

* Fig. XXIX.

groups, in which they were so closely approximated and showed structural characters so far removed from "normal" astrocytes that at best only an opinion, and that by no means certain, could be given that the appearances denoted amitosis in the neoplastic cells.

The second case of glioma was of the fibrous type and first showed symptoms twelve months before death. During the last five or six weeks of life while the patient was under observation in hospital the cerebral lesion manifested no progressive changes and therefore a diagnosis of tumour could not be made with certainty. Death was due to an acute left sided oedema of the lungs.

At autopsy a large carcinoma was found on the posterior wall of the stomach, but no secondary growth had occurred in the neighbouring lymph nodes or in the liver. A tumour about 5 cm. in diameter was /

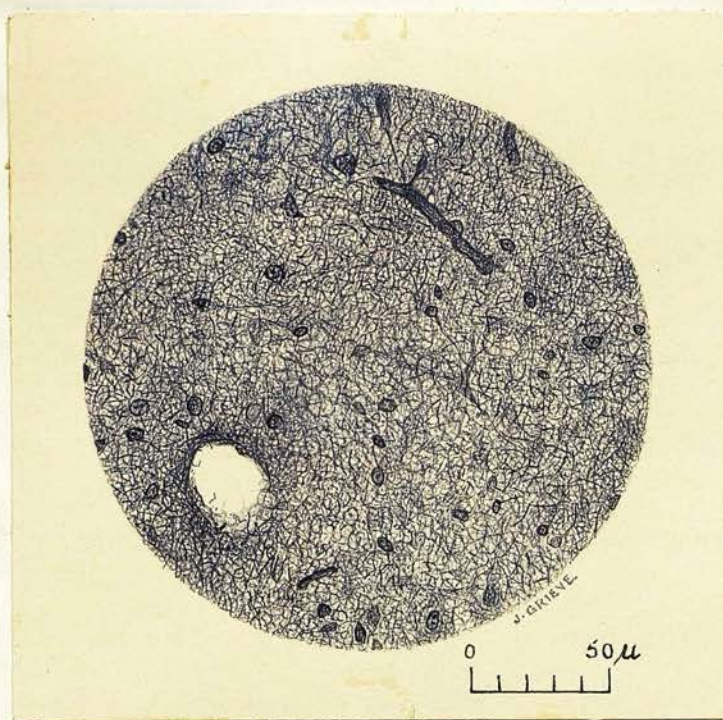


Fig. XXX. - A portion of a glioma taken near the periphery. The tumour has become quiescent and consists throughout of a thick feltwork and fine neuroglial fibres. The nuclei of the tumour are scanty.

(Frozen section stained by Holzer's Krystall-Violett Method).

was found in the neighbourhood of the right thalamus. It was sharply demarkated, showed no necrosis, and was avascular and so hard to touch that it was diagnosed as a fibroma (astrocytoma).

Microscopic examination demonstrated that the cerebral neoplasm was composed of a thick felt-work of fine neuroglial fibres. The neoplastic nuclei were few in number, were fairly regularly distributed over the microscopical field, were rounded and of fairly regular size.* In sections impregnated by gold, some astrocytes were seen which had reached a high degree of structural perfection, but around most of the nuclei no delimited cell body was demonstrable. In the neighbourhood of the glioma a certain amount of gliosis had occurred. This change had taken place in foci and was not diffuse.

The case therefore was one of a glioma in which /

* Fig. XXX!

which the astrocytes had developed numerous fibres and then had undergone regressive changes. In this connection the astrocytes had progressed through those stages of non-neoplastic astrocytes which eventually lead to gliosis. Moreover, the gliosis had occurred in the tumour and it had had little effect on the neighbouring brain tissue; the case was doubtless an example of a regressing glioma.

A glioma may consist of a syncytium throughout. One of the cases referred to previously, namely a glioma of the cervical portion of the spinal cord, is an example of this type, and, as noted, the series contains another similar case of cervical glioma. In both these cases the tumour grew quickly, the patients living only six and eight months respectively after the first manifestations appeared. This can be easily understood since the syncytial tumour exerts /

exerts its whole energy in growth and none in differentiation.

A case in the series, however, showed the fact that even a syncytial glioma may remain quiescent for a number of years. Although I am ready to believe that this is an exception, the case is so instructive from the viewpoint of the pathology of tumours that it is interesting to give the following short history.

J.H., a miner, aged 42, for the first time took a fit in December, 1926. The following February he was admitted to Professor Bramwell's Ward. From the clinical history, mode of attack and the investigation there, a tumour in the neighbourhood of the gyrus centralis posterior was diagnosed. The patient remained three weeks in hospital and during this time had two fits. He was then allowed home and treated with luminal. The fits decreased in number and severity and the patient remained fairly well until December, 1930. Then the fits recurred and he developed marked loss of power in the right hand.

On January 31, 1931, he was re-admitted to hospital in a semi-conscious state and with paralysis of the right side. On the evening of February 5 a cerebral hemorrhage occurred and he died the following morning.

Autopsy:- Fairly well demarkated tumour of about 3 cm. in diameter was found immediately under the cortex /

cortex in the neighbourhood of the left gyrus centralis posterior; the centre of the tumour was cystic; the peripheral portions were firm. A second tumour was present in the neighbourhood of the left pedunculus cerebri, and it was into this that the fatal hamorrhage had occurred.

Microscopic Examination:- The tumour in the gyrus centralis posterior was composed of a syncytium; nowhere had individual cells differentiated out. Around the tumour areas of gliosis had formed an incomplete capsule; the non-neoplastic astrocytes in the neighbourhood showed no sign of proliferation.

In the second tumour, namely that in the left pedunculus cerebri, were demonstrated astrocytes which had reached a high degree of structural perfection.

It should be noticed that in certain cases of the series astrocytes were seen which had differentiated out of the neoplastic syncytium; moreover, in certain of these cases the neoplastic astrocytes had reached a high stage of structural perfection.

The question arises do these neoplastic astrocytes undergo further division and thus give rise /

rise to daughter cells? It is impossible to give a certain answer to this question. Several difficulties arise in the solution of the problem. Necrosis is so widespread that it is often impossible to determine the particular degree of structural development which the older parts of many gliomata have reached. In the minority of cases of the series in which the neoplastic astrocytes showed a high degree of structural perfection in their older parts, the cells were not only large but numerous. This, however, is in accordance with the fact observed in the microscopical preparations that when individual cells differentiate out of the neoplastic syncytium, a large number of individual cells are formed.

It is a well-known fact that the non-neoplastic astrocyte has retained to a very high degree the power of reproduction and in many cases of damage /

damage to the brain astrocytic proliferation is not only very marked but spreads to a great distance around the damage. As a result new formed astrocytes occur in great numbers. Division of the astrocytic nucleus occurs only by amitosis. This is a fact recognised by all investigators and my experience confirms it. I have never observed mitosis in astrocytes however quickly they are reproducing.

It is by no means easy in human tissue obtained at autopsy to demonstrate with absolute certainty the different stages of amitosis in non-neoplastic astrocytes, even when proliferation is in progress. It is therefore easy to understand that the difficulty is much greater in the case of neoplastic astrocytes.

It may be maintained that growth by pressure indicates a proliferation of the neoplastic cells /

cells which lie deep in the tumour. Such a conclusion, however, would be incorrect. The syncytium itself can exert a considerable pressure. In one of the cases already described, the tumour had invaded the pia-arachnoid spaces and pushing the dura mater in front of it had made deep pockets between the transverse processes of several vertebrae.

I am inclined to believe that in those gliomata which have a syncytial periphery the spread of the growth is for the most part an increase of the syncytial protoplasm and not through division of the differentiated neoplastic cells.

2. Proliferation of the astrocytes in those parts adjacent to gliomata:-

In all the cases of the series there had occurred proliferation of the astrocytes in the tissue surrounding the glioma.

It has been already recorded that in

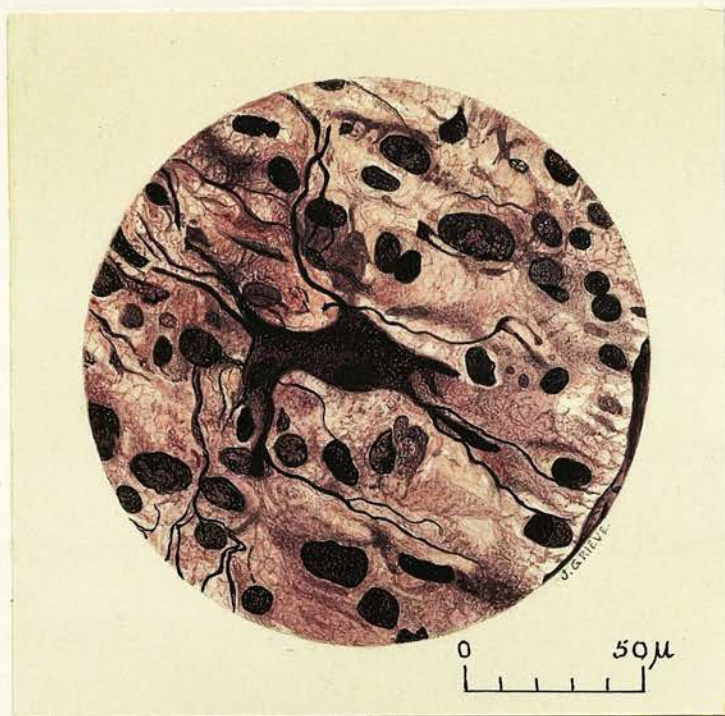


Fig. XXXI. - From the marginal portion of a glioma.
A non-neoplastic astrocyte has been enclosed by the growing syncytial margin of the tumour; it is swollen and its processes are undergoing disintegration. ("clasmotodendrosis").

(Frozen section impregnated by Cajal's Gold Chlorate Sublimate Method.)

two cases of quiescent tumour, namely that of a syncytial glioma and that of an astrocytoma, reaction had occurred around the neoplasm of the proliferated astrocytes; fibres had been formed and the cells had regressed. In the other cases the neoplasms were in the process of growth and the surrounding astrocytes were actively proliferating. As the tumour advanced there occurred a correspondingly advancing zone of proliferating astrocytes; when the advancing neoplastic zone involved these astrocytes they underwent necrobiotic changes which led to their degeneration and disappearance. These appearances are exactly the same as in all cases of advancing degenerative processes of the central nervous system.

It was found that the proliferation of the "normal" astrocytes occurred over an area which extended widely from the neoplastic zone, and moreover /

* Figs. XXVIII & XXXI.

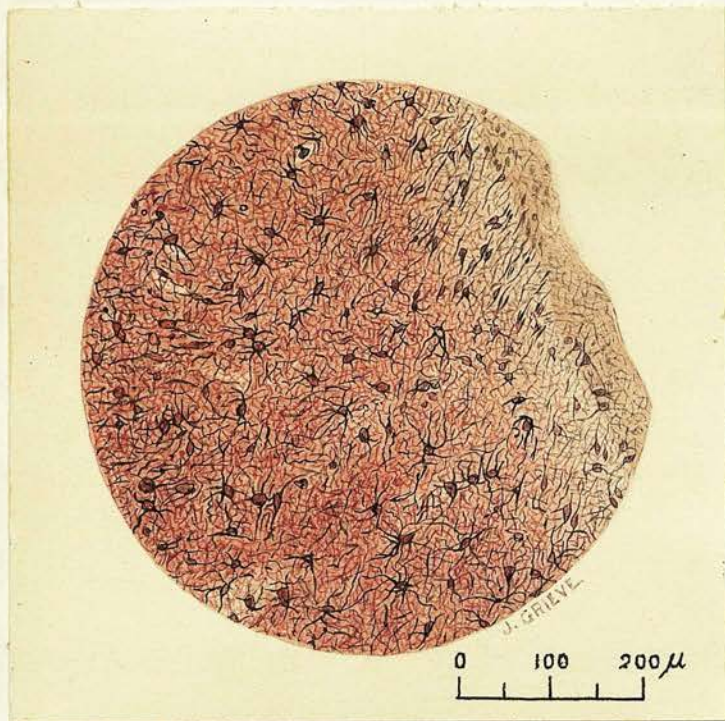


Fig. XXXII. - From the brain at a distance from the growing syncytial margin of a glioma. The pre-existing (non-neoplastic) astrocytes have proliferated profusely and over a large area. The new formed astrocytes are not only numerous but also large. In the right upper portion of the field the membrana limitans superficialis is seen.

(Frozen section impregnated by Cajal's Gold Chlorate Sublimate Method.)

Moreover the proliferation was profuse.* In the case of cervical glioma, I have stated that the proliferation of the neighbouring astrocytes is not a transition of these cells to a neoplastic phase, and further I have given the opinion that the proliferation is not an expression of a protective mechanism on the part of the surrounding non-neoplastic tissue, but is an example of the general rule that wherever damage or destruction of the tissue occurs, there takes place a proliferation of those cells which have retained the power of division. The study of all this series of cases confirms this contention and this opinion.

Moreover, it is found that in the neighbourhood of the glioma not only does the fibrous type of astrocyte proliferate, but also the protoplasmic type.

From what has been said it is to be understood /

* Fig. XXXII.

understood that astrocytic proliferation occurs not only around gliomata, but around other neoplasms and injuries. I have investigated two cases of carcinoma secondary in the brain; both showed proliferation of the surrounding astrocytes although in neither of these cases was the appearance so marked or so widespread as in cases of gliomata; the proliferation occurred only in certain small foci in the neighbourhood of the new growth.

I have investigated a third case of a non-gliomatous neoplasm. This occurred in a patient of 13 years and was composed of round cells with large hyperchromatic nuclei which varied little in size. The neoplasm may have been a neurocytoma but as sections impregnated according to Gross-Bielschowski's silver method showed no nerve fibres and since the cells showed no other structural characteristic by which /

which it was possible to determine their nature it is preferable to classify it by the indefinite and comprehensive term of "teratomatous-like" tumour. In this case the proliferation of astrocytes was widespread and profuse. This marked proliferation of the astrocytes in the neighbourhood of the tumour is probably to be accounted for by the age of the patient: growth is a characteristic of youth and proliferative changes in cells are often much more evident in the early years of life.

With a view to determining the degree and the type of response of the interstitial tissue of the central nervous system to traumata, I carried out a number of animal experiments, the results of which can be briefly stated in so far as they have a bearing on the present problem. Rabbits were chosen because of the relative ease with which the brain could /

could be reached and because they are readily procured in large numbers.

In the first group, after the skull had been opened, the cortex was pierced to a depth of .5 cm. by a sharp needle and animals were killed at intervals of 24 hours up to 14 days. Sections were prepared in a similar manner to those of the neoplasms under review, and it was found that a proliferation of astrocytes had occurred which in 24 hours was limited to an area immediately around the injury and which by 48 hours had spread until almost the whole hemisphere was involved, whereas the specimen obtained at the end of 14 days was little different from that after 48 hours. That is to say, that the reaction to the trauma was immediate and had become maximal after an interval of only 48 hours.

In the second group it was decided to
damage /

damage the brain by means of a cautery instead of a wound, and the animals were killed at similar intervals. On this occasion very little reaction had taken place in 24 hours, a slight reaction in 48 hours and by 72 hours the response was maximal and as widespread as in the first group. Thus the only difference between these types of trauma was in the time taken to stimulate the astrocytic response. From these experiments it would be seen therefore that once the necessity for a defence had arisen the amount or the degree of the reaction was not controlled by the type of injury but was determined more by the capacity of the tissues to respond.

A third group of animals, which might be regarded as a control was used in this connection. In these the skull was opened as before but the skin sutured without damaging the brain. In all the sections /

sections examined in this group no proliferation of astrocytes was seen, which enabled one to say definitely that the mere opening of the skull itself did not produce a reaction unless the brain was actually damaged.

From the point of view of diagnosis, the importance of recognising the secondary proliferation of "normal" astrocytes in the neighbourhood of gliomata is self-evident. In the examination of small pieces of tissue from parts which show these changes - and it is often only a very small piece of tissue that the operating surgeon can give to the pathologist for him to investigate - the erroneous conclusion may well be made that the tissue is neoplastic and that the glioma therefore is composed of astrocytes which have reached a high degree of structural differentiation. Moreover, it must be remembered /

remembered in this connection, that many non-neoplastic astrocytes in cases of rapid proliferation show a wider departure from the "normal" structure than do many neoplastic astrocytes. Therefore the study of single cells cannot reveal whether they are neoplastic or not. Their true nature can only be diagnosed from their position in relation to the neoplasm and to the non-neoplastic tissue.

3. The Occurrence of Necrosis:- In the central older parts of the glioma necrosis is a usual occurrence, and in most cases is so marked that it is recognisable by the naked eye. Owing to the liquefaction of the necrotic tissue, cysts occur; their walls are composed of neoplastic tissue. These changes are so well known that for a long time they have been regarded as a characteristic appearance of gliomata.

III.

Necrosis without cyst formation not only occurs in those gliomata which are composed of differentiated elements, but also in those composed throughout of a syncytium. One of the cases of cervical glioma and the case of syncytial glioma of the gyrus centralis posterior are examples of this occurrence.

Microscopical areas of necrosis were frequent in the growing syncytial margins of the gliomata in the series. Further, since numerous disintegrating nuclei were found in these portions of the tumour, necrobiotic changes were widespread through the whole syncytium.

Lastly, necrosis occurs in the non-neoplastic tissue around the growing glioma and which has not yet been invaded by the tumour. Many of the cases gave an example of necrosis and of disintegration /

disintegration of the pre-existing non-neoplastic astrocytes in the zone bordering on the syncytium.

Thrombosis of blood vessels, with consequent diminution of the blood supply is probably a factor in the occurrence of the marked necrosis in the substance of the glioma. In general, however, the occurrence of necrosis in the tumour is not solely dependent upon the diminution of the blood supply; other factors as yet unknown play a part. Certainly the small foci of necrosis and the degeneration of the nuclei which occur through the whole syncytial margin of a glioma cannot be explained merely by a disturbance of the blood supply, nor yet the necrobiotic changes of the astrocytes in the neighbouring zone. As mentioned before, it is possible that during quick growth of the tumour the mechanism in the brain and spinal cord for draining away the effete products of metabolism /

metabolism is insufficient to deal with the greatly increased mass of tissue. Hence the fluid bathing the tissues and the fluid in the peri-vascular spaces is saturated with effete metabolic products. Further, it is a well known fact that the chemical composition of this used product of tumour cells differs from that of "normal" tissue.

It appears justifiable to suggest that the presence of an excess of used metabolic products, together with perhaps their altered chemical composition is answerable not only for the damage to the endothelium lining the blood vessels - a condition preliminary to thrombus formation - but also for the necrosis in the syncytial margin and in the surrounding brain tissue.

4. The Occurrence of Hemorrhage:- The occurrence of larger and smaller hemorrhages in gliomatous tissue is /

is a further characteristic of this type of tumour. It is well recognised that the hæmorrhage may be so massive that it quickly leads to the death of the patient; on the other hand little hæmorrhages may occur and these appear often multiple and not single. Lastly, the hæmorrhages in the tumour may be only seen on microscopical examination.

Examples of all these types occurred in my series.

Hæmorrhage may occur not only in the glioma but also in the non-neoplastic tissue in its neighbourhood. Here also, the hæmorrhage may be massive or small. In two cases death was brought about by a hæmorrhage in a part distant to the tumour. In both cases the glioma was in the left cerebral hemisphere. In the first case the hæmorrhage had occurred into the cerebral peduncles and pons /

pons, and in the second into the pons. It should be noticed incidentally that in neither of these cases was there a second tumour into which hæmorrhage had occurred.

In the case of a large glioma of the left cerebral hemisphere, numerous petechial hæmorrhages had occurred in the cortex and into the sub-cortical tissue of the temporal lobe on the side opposite to that in which the tumour was situated. Microscopical examination demonstrated that no gliomatous tissue was present in the region of the hæmorrhages.

A massive hæmorrhage into a glioma may occur through the rupture of a fairly large blood vessel in a necrotic portion of the tumour, or by a rupture of an aneurysm which has occurred there. Further, massive hæmorrhages, as also the small hæmorrhages which are usually present in a glioma, may /

may be brought about owing to thrombosis of the blood vessels in relation to the tumour.

One of the cases of syncytial cervical glioma showed a further condition which could give rise to hæmorrhage. A portion of the tumour had become cystic and the wall of the cyst presented, over a fairly large surface, new formed blood vessels which gave the appearance as though the lining of the cyst was formed of granulation tissue. It is easy to understand that in this condition hæmorrhage into the interior of the cyst may readily occur.

It is possible that large, fatal hæmorrhages occurring at a distance from the tumour have a relationship to thrombosis at the site of the hæmorrhage, but this is a point which is difficult to prove.

In all cases whether hæmorrhage occurs owing to rupture of a blood vessel, owing to rupture of /

of an aneurysm or following a thrombosis, damage to the arterial wall must have preceded the occurrence.

As discussed under the heading of "The Occurrence of Necrosis", I am of the opinion that metabolic products are the most probable factor in causing a local injury of the vessel wall; these products strengthened by the abnormal products of tissue necrosis, especially in large rapidly growing gliomata, are doubtless in the peri-vascular spaces of blood vessels in the tumour and in parts of the brain distant from it, and present therefore a possible explanation for the damage in these places.

The numerous hæmorrhages which occur near the tumour are probably to be explained in the same way as those in cases of acute infections. I suggest again that hæmorrhages related to a glioma are dependent on metabolic or other products of neoplastic tissue.

5. Nomenclature and Classification:- Since much of the work on gliomata which has appeared during the last few years perhaps especially in English and American periodicals deals with the nomenclature and classification of these neoplasms I wish to expand a little upon this, but especially to discuss the wisdom of accepting finally the elaborate classification of any one author until complete proof is available that multiple terminology subserves a useful purpose either clinically or pathologically.

The great pathologist, Hugo Ribert³², says concerning the name "spongioblastomata" given to that type of neoplasm which has as its prototype the spongioblasts of the developing neural tube, "One must not forget that these tumours are genetically identical with those formed of true glia The true gliomata are really therefore differentiated spongioblastomata" /

spongioblastomata" (By "true glia" he means astrocytes). Investigation of this series of gliomata has demonstrated that tumours may consist not only entirely of a syncytium, but also that in the same neoplasm all stages of structural differentiation occur, from the simplest, the syncytium, to the most complicated, the well formed astrocyte.

Pathology seeks to elucidate the processes in living tissue which constitute a disease. If the separation of gliomata into different classes - be they many or few - leads to a better understanding of their course, of their origin, of their growth and of their biological properties, then it is one of the functions of pathology to classify them. If, on the other hand, their classification adds nothing to our knowledge of these problems, it is useless from the point of view of pathology.

Penfield³³ constantly points out that an essential to the intelligent use of any classification of gliomata is a knowledge of the developmental and pathological forms of normal neuroglia and of the behaviour of the neuroglia under various conditions.

He has been able in consequence to modify considerably the original classification of Bailey & Cushing.³⁴

Penfield submits that eight types are quite sufficient, namely:-

- | | | | |
|-----|---------------------------|-----|-----------------------------|
| (1) | Neuroepithelioma. | (2) | Spongioblastoma Multiforme. |
| (3) | Astrocytoma | (4) | Ependymoma |
| (6) | Astroblastoma | (5) | Medulloblastoma |
| (8) | Unipolar Spongioblastoma. | (7) | Oligodendroglioma. |

Although this classification is a very distinct improvement on that much more unwieldy one of Bailey & Cushing, it would seem that even yet it is much too elaborate, especially when one remembers for instance that development is a continuous process and that there is no hard and fast line between the polar spongioblast /

spongioblast and the astroblast or between the astroblast and the astrocyte.

From a clinical point of view it would be necessary in making a classification of any given tumour to search for the general stage of differentiation reached and to remember that except in spongioblastoma multiforme neuroglial differentiation has no sharply distinct stages. Neuroglial cells differ in form according to the part of the brain in which they are found.

Since for obvious reasons this formula for making classification is impracticable, I would suggest that a better understanding of gliomata is reached if one studies them as biological problems rather than divides them into single and special categories which are more or less only artificial.

S U M M A R Y.

1. The embryological development of the interstitial tissue of the central nervous system was demonstrated and discussed.
2. Certain clinical problems in diagnosis were debated, and these were discussed with especial reference to the cases in the series.
3. A series of 25 cases of gliomata were investigated. In 2 cases the growth had been quiescent for several years; in the remainder growth was active.
4. In the majority of cases the growing margin of the glioma consisted of a syncytium or of a syncytium from which single cells were differentiating. In the other cases the neoplastic margin was composed of large and immature astrocytes. Many syncytial nuclei showed necrobiotic changes.
5. For the most part the neoplasms were growing by infiltration /

infiltration into the surrounding tissue, but notably in one case the tumour, or part of it, was growing by pressure.

6. In 3 cases the glioma consisted throughout of a syncytium; one of these had remained quiescent for four years.

7. Some of the cases showed all stages of differentiation from a syncytium to an astrocyte which had reached a high degree of structural development.

8. It is uncertain whether neoplastic astrocytes which have reached a high degree of structural perfection are able to multiply.

9. In all cases the pre-existing non-neoplastic astrocytes in the neighbourhood of the glioma had proliferated; this proliferation was often marked and widespread.

10. Reaction of the interstitial tissue to injury as seen /

seen in animal experiments and also non-gliomatous tumours was described and discussed.

11. Necrosis was found not only in the old parts of the neoplasm but also in the growing marginal parts and the surrounding tissue; an explanation of this was made.

12. Haemorrhages occurred in different degrees from those which were microscopical in size to those which were massive and fatal. In certain cases the haemorrhage occurred at a distance from the neoplasm.

13. The modern tendency to multiply nomenclature and classification was criticised from both its clinical and pathological standpoints.

14. It was submitted that a better understanding of gliomata is reached if they are studied as biological problems.

APPENDIX

Technical Methods Employed.

Aniline dyes stain neuroglial nuclei but show the perinuclear cytoplasm only in a general way. Occasionally certain astrocytes in a very active phase of reproduction are demonstrated. Weigert's neuroglial staining method demonstrates the nuclei and the glia fibres. For the demonstration of the whole astrocyte it is necessary to use Cajal's Gold Chloride Sublimate Method.

For the details of technique of this method I have referred especially to those articles dealing with it by S. Ramon y Cajal, E. Romeis, W. Speilmeyer and C. Da Fano.

Many authors of the latest papers on neuroglia maintain or imply that the Gold Chloride Sublimate Method is variable and difficult. This is not true. According to my experience of this method extending now over several years, I can say emphatically that the technique gives such universally constant results that it can be carried out in every histological laboratory, provided that scrupulous attention is given to the chemical purity of the reagents and to the cleanliness of the apparatus. My experience is that not only routine work in gliomata can be well carried out but that the preparations made according to this method are constant.

The Gold Chloride Sublimate Method has certain limitations. It does not demonstrate, for example, the structure of a glioma composed of "mature" astrocytic fibres. In this case the negative picture obtained must be converted into the positive picture by Weigert's Glia Method or by one of its modifications, e.g. Holzer's Krystall-Violett Method; further, the nuclei and the protoplasm of a neuroglial syncytium are not demonstrated. The negative picture obtained by these methods must be supplemented by the picture obtained from Hamatin and Eosin preparations and by sections impregnated by the different silver methods.

The use to which the different methods are put to demonstrate the structure of gliomata is indicated in the illustrations.

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