THE GLIOMA GROUP STUDIED BY ORDINARY HISTOLOGICAL METHODS.*

BY

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FROM time to time attempts have been made to subdivide the glioma group. In 1912 Tooth¹ of the National Hospital, Queen Square, showed that clinical malignancy was associated with the presence of enlargement of the glia cells, numerous mitoses, and hyperplasia of the vascular endothelium. The most important contribution, however, is that of Percival Bailey and Harvey Cushing,² who in 1926 introduced an entirely new classification of the gliomas. This was based partly on an examination of Dr. Cushing's unrivalled collection of brain tumours by means of the methods devised by Ramón y Cajal, del Río Hortega, and the other members of the brilliant Spanish school of neuro-histologists, and partly on the correlation of the pathological picture with the clinical course. The study revealed that some of the subgroups were to all intents and purposes innocent, while others were highly malignant.

There were fourteen of these subgroups, each composed, for the most part, of one type of cell met with during the development of the brain. The classification is therefore an embryological or histogenetic one, and the cells are recognized by their reaction to the special gold and silver stains (gold sublimate and silver carbonate) introduced by the Spanish neuro-histologists. It is the object of this paper to show that the important types of tumour can be recognized by ordinary histological methods, and without the aid of the difficult and specialized gold and silver methods. In addition to haematoxylin and eosin, however, Mallory's phosphotungstic acid haematoxylin should always be used, for it stains both the neuroglia fibrils and many of the protoplasmic prolongations of the cells, so that the picture becomes much more clear-cut and characteristic.

To master the fourteen groups of Bailey and Cushing is nearly as hard as to master the fourteen points of President Wilson. But in several of these only one or two examples have been described, and others may be fused into larger groups. For the purpose of this paper only a few of the main divisions will be considered.

As the basis for classification is an embryological one, a word or two must be devoted to developmental matters. The interstitial tissues of the central nervous system consist of three main elements—namely, the astroglia, the oligodendroglia, and the microglia. The microglia is mesodermal in origin, and is therefore not truly a part of the neuroglia. So far, no tumours have been recognized as arising from this tissue. Tumours may arise from the oligodendroglia, but very few have been recognized, and as I have no experience of them they will not be discussed here. We are left, therefore, with the astroglia and the cells from which it originates.

The epithelium of the medullary groove is the starting-point of the entire central nervous system. From this there arise two very different sets of cells: (1) spongioblasts, elongated cells which form the spongework or interstitial tissue of the nervous system; and (2) neuroblasts, rounded cells which develop into neurones. In addition, there is a third group of "undifferentiated cells" regarding which little definite is known. They may remain undifferentiated, being known as medulloblasts, or they may become differentiated into neuroblasts or spongioblasts. It may be that the oligodendroglia arises from some of these cells. We are concerned here only with the undifferentiated form, the medulloblast. To return to the other two main branches of the parent stem, the primitive spongioblast develops first into a bipolar spongioblast and then into a unipolar spongioblast. This in turn gives rise to an astroblast. The astroblast is distinguished from the spongioblast by the development of numerous processes, one of which becomes attached to a vessel wall and is

known as the "sucker-foot." Fibrils appear in the protoplasmic processes, and the cell now becomes an astrocyte, which is the adult classical neuroglial cell. Some astrocytes do not develop fibrils. These are called protoplasmic astrocytes, in distinction to the ordinary or fibrillary astrocytes. The change from the astroblast to the astrocyte takes place about the fourth month of foetal life. Some of the primitive spongioblasts remain attached to the ventricular wall, and are then called ependymal spongioblasts. When these lose their peripheral processes they become changed into the cuboidal cells of the ependyma. Both ependymal cells and ependymal spongioblasts contain tiny rods, known as blepharoplasten, by which they can be recognized.

Any one of the cells just enumerated may form the principal constituent of a glioma, so that there have been described spongioblastoma multiforme, spongioblastoma unipolare, astroblastoma, astrocytoma protoplasmicum, astrocytoma fibrillare, ependymoblastoma, ependymoma, etc. It must be kept in mind that many of these are but slight variations of the same theme, and, as Ewing remarks, it appears premature to urge the full adoption of this very complex classification. It seems better to wait until general usage has made its selection of terms and classes. Further, these types are not always pure. In my own experience I have found a spongioblastoma combined with an astrocytoma, an ependymoma with an astroblastoma, and an astroblastoma with a spongioblastoma. These transitions can be more readily examined in autopsy material, where the whole tumour is available, than in fragments removed at operation. Moreover, a slowly growing astrocytoma may become changed by irritation into a rapidly growing spongioblastoma.

The fundamental contribution of Bailey and Cushing is not a mass of names, but the demonstration that variations in histological structure correspond to variations in malignancy. At one end of their list of 492 gliomas there are the medullo-epitheliomas, in which the average survival period was eight months, while at the other end are the fibrillary astrocytomas, in which the average survival period was eighty-six months, some of the patients living for many years. Removal of such a tumour may be followed by a complete and lasting cure. Speaking generally, the more primitive the cell type, the more malignant is the tumour. Thus the medulloblastoma and the spongioblastoma are highly malignant, while the astrocytoma and the ependymoma are relatively benign.

This paper is based on a study of 31 gliomas obtained in the post-mortem room. All the principal types are represented, and these alone will be considered. The grouping is as follows:

Astrocytoma	...	16	Ependymoma	...	1
Spongioblastoma	...	9	Astroblastoma	...	1
Medulloblastoma	...	3	Unclassified	...	1

Most gliomas can be placed in one of the three main groups of astrocytoma, spongioblastoma, and medulloblastoma. The ependymoma is rarer, and the astroblastoma still more rare. In Bailey and Cushing's series the astrocytomas and spongioblastomas were present in equal number, while in my own material there were twice as many of the former as the latter.

Astrocytoma.

This tumour, in its fully developed form, may be regarded as innocent in type. Many of Cushing's patients were alive years after removal of the tumour; the average survival period was over six years. Growth is slow, so that even without operation the course may be a prolonged one. Its benign character is explained by the adult type of cell of which it is composed. It is not suggested by the gross appearance, for the tumour is even less well demarcated than the spongioblastoma from the surrounding tissue, and merges insensibly with the normal brain. Moreover, it may attain a great size. In one of my cases the entire frontal lobe was occupied by the tumour. It occurs in the hemispheres both of the cerebrum and cerebellum—the former usually in adults, the latter in children. Cyst formation is common, although the reason is obscure. The cyst fluid is often under distinct pressure, which

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would not be expected if the process was merely a degeneration. The only alternative seems to be that the fluid is produced by the tumour tissue. Many cerebellar cysts are of this nature. The tumour may disappear, except for a small nubbin attached to the wall of the cyst. In one of my cases even this could hardly be detected.

The microscopic picture in a typical case is very characteristic, and can be recognized at a glance. Excellent examples may be seen in Tooth's paper. The cells as a rule are few in number, and are separated by a dense network of glia fibrils, which are well stained by phosphotungstic acid haematoxylin, and which supply the chief diagnostic feature. In other cases the tumour may be much more cellular, and occasionally I have found it difficult to draw with certainty the line of distinction between astrocytoma and spongioblastoma. The cells (astrocytes) and their nuclei are usually spherical, but may be elongated. There is a complete absence of mitotic figures. Nerve cells may remain intact, surrounded by tumour tissue. Although this is occasionally seen in other gliomas, I have found it very suggestive of astrocytoma. The surrounding tissue does not show any gliosis, thus differing from the more malignant forms of glioma. It is therefore difficult to determine with certainty the limits of the tumour. Calcification is fairly common, and may be detected clinically by means of x rays. It is best marked in the walls of the vessels, but it is not confined to this position. In one case lime salts were present in the brain tissue surrounding the tumour.

By means of gold impregnation it is possible to show that some tumours are composed mainly of fibrillary astrocytes, while others consist of protoplasmic astrocytes. Bailey therefore speaks of astrocytoma fibrillare and astrocytoma protoplasmaticum. It is difficult to make this distinction in phosphotungstic acid haematoxylin preparations, and, as nothing seems to be gained by doing so, I have not attempted to separate these subgroups.

Spongioblastoma Multiforme.

The spongioblastoma is the most common tumour in Bailey and Cushing's series, although not in my own. It is perhaps the most malignant of all the gliomas, and corresponds to the gliosarcoma of the older literature. The onset is rapid and the course brief. In addition to the ordinary form, named spongioblastoma multiforme by Globus and Strauss³ in 1925, because of the variety of the cells which compose it, a more rare type, known as spongioblastoma unipolare, has been described. This is composed mainly of unipolar spongioblasts. The tumour is widely invasive, and recurs after removal. It may give a false impression of encapsulation, because degeneration and softening may cause the central part to become separated from the firmer peripheral part of the tumour. As a rule it is softer than the astrocytoma, being cellular rather than fibrillar in structure. It also differs from that tumour in being usually confined to the cerebral hemispheres. In one case it grew from the septum lucidum and separated the lateral ventricles. Not infrequently it is multiple. The several tumours should be regarded as an expression of multiple centres of origin rather than as metastases.

The microscopic appearance is very different from that of the astrocytoma, although borderline cases occur in which a distinction is very difficult. The chief characteristics of the tumour are its cellularity and the multiform character of the cells. Three main types of cells may be distinguished: (1) oval, pear-shaped, or elongated cells; (2) undifferentiated round cells; and (3) giant cells with numerous nuclei, often bizarre in arrangement. Mitotic figures are numerous and often atypical. Indeed, there is no tumour in which cell division can be more readily studied. There are no glia fibrils—in sharp distinction to what is seen in an astrocytoma. The tumour is very vascular, and haemorrhages are frequent. Proliferation of the vascular endothelium is a very characteristic feature, and large masses of these cells may be formed. In one case seven or eight mitotic figures could be seen in the endothelial cells in one field. As a result, the lumen of the vessel may be closed, and this may partly account for the frequency of degenerative changes. In some of the cases

this change was observed in the surrounding brain tissue, as if the endothelial hyperplasia were preceding the spongioblastic proliferation. There may also be proliferation of the adventitial cells. Outside the tumour there is often a proliferation of astrocytes. These may assume the form of giant glial cells, but these irritation forms are never multi-nucleated, and are totally different from the giant cells of the tumour.

It is not so easy to be certain of the origin of the spongioblastoma as in the case of the other forms of glioma. The elongated and pyriform cells appear to be spongioblasts, but the giant cells present a problem which has not yet been solved. Globus and Strauss consider that the giant cells are unripe and highly atypical spongioblasts, but this appears very doubtful. According to Bailey, the multiplicity of structure is largely due to degenerative and reparative processes. More study is needed of this group, and it may be that the proliferation of the vascular endothelium may prove to play a more fundamental part than has hitherto been suspected.

Medulloblastoma.

As this tumour arises from one of the most undifferentiated of cells, the medulloblast, it is one of the most highly malignant of the gliomas. It usually occurs in children, but one of my two patients was an adult. In a child it is likely to be in the roof of the fourth ventricle, usually in the vermis of the cerebellum, while in the adult it is more likely to grow from the cerebrum. The tumour is soft and reddish-grey in colour. It may invade the sub-arachnoid space, giving rise to one form of the condition known in the literature as diffuse sarcomatosis of the meninges.

The microscopic picture shows an almost complete lack of differentiation, and suggests a round-cell sarcoma. The fibrils of the astrocytoma and the cellular variety of the spongioblastoma are both lacking. The cells are for the most part round, but some may have a tail like a carrot. In places there may be a pseudo-rosette arrangement, the cells being collected in groups, often around a small vessel. The tails of the cells are directed towards the centre, and as these tails stain poorly it may appear as if the nuclei were arranged round a clear space, but there is no true lumen. In addition to the undifferentiated cells, both spongioblasts and neuroblasts may be seen in silver carbonate preparations. It is this indication that the cells are bipotential which justifies the assumption that the tumour arises from the medulloblast, a cell which cannot of itself be recognized morphologically.

Ependymoma.

Bailey describes two types of tumour: the ependymoma, consisting of adult ependymal cells, and the ependymoblastoma, composed of ependymal spongioblasts. These will be considered together. Like the medulloblastoma, this tumour also usually arises in relation to the roof or the floor of the fourth ventricle, but it may grow from the wall of the lateral ventricles, the aqueduct of Sylvius, or the central canal of the cord. It is considerably firmer than the medulloblastoma. The cells of which it is composed are usually well differentiated, and the tumour is of slow growth and low malignancy. Calcification is common.

Microscopically the tumour is composed of cells which are tadpole-shaped, with a single heavy tail. These cells may be grouped around a small lumen, just as normally they are grouped around the ventricular cavity. To this arrangement the rather misleading name of true rosette is applied. The presence of these little canals is very characteristic of an ependymoma, and is not seen in any other form of glioma. The tiny rods (blepharoplasten) are seen between the nucleus and the lumen, and are quite characteristic of ependymal cells.

Astroblastoma.

This is a rare tumour, but it is included here because its appearance is so characteristic. It occurs in the same situations as the astrocytoma, but is composed of a more primitive cell, the astroblast. This cell is characterized by the possession of one large sucker-foot, which is attached

to a blood vessel; it is not sufficiently developed to form fibrils. The tumour cells are for the most part grouped around vessels to which they are attached by the sucker-foot, so that the condition can be recognized at a glance. Although normal astrocytes are attached to the vessel wall, in the astrocytoma this arrangement is not at all evident, whereas in the astroblastoma it is the chief feature of the tumour.

Conclusion.

It has been shown that the gliomas can be divided into a number of distinct groups by the aid of ordinary histological methods. This subdivision is of real importance, because the tumours differ not only in their microscopic structure but also in their clinical behaviour. At the same time it is well to realize that this classification is in no way final. It is based upon the resemblance which the tumour cells bear to certain of the more embryonic glial cells. When the histological picture is typical, the recognition of the group to which the tumour belongs is very easy. In other cases it is difficult or even impossible to decide how to classify the tumour. It is in such cases that the special gold and silver methods of staining place so powerful a weapon in the hands of the pathologist, for by means of them the minute morphology, and in particular the processes and fibrils of the cells, are brought into prominence. In the majority of the gliomas, however, the ordinary methods of histology are sufficient for diagnosis and classification.

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THE VALUE OF X-RAY DIAGNOSIS IN MEDICO-LEGAL CASES.*

BY

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THE use of x rays in medico-legal cases began shortly after their discovery. Unfortunately the first legal cases that occurred were due to burns caused by the rays. Later on, x-ray evidence was called in to help in legal cases where the patient had suffered a fracture, and the x-ray plate was allowed as evidence of the fracture. A time came when the operator who made the actual roentgenogram was hailed to court to swear that the radiograph shown as evidence was really the one he had taken. During this phase of the law I spent a whole day in court to give evidence, and though I would swear that the roentgenogram was that of the patient and that it had been made in my department, I had not actually pressed the button when the x rays were used, and therefore the judge would not allow me to give evidence.

It is seldom now that the radiologist is called upon to testify that he made the picture. In a large department with several technicians making several dozen films a day it would not be possible to be certain that a technician would remember the actual making of the radiograph in question, and frequently after he has made the exposure he does not even see the finished film, and cannot therefore swear that it was made by him. Such technicalities are now waived, and the word of a responsible doctor is accepted that the film under consideration is the film of the patient required.

As already mentioned, the first medico-legal aspect of x rays was due to the burns caused by x rays. The earliest reference I have been able to find is a report in the *British Medical Journal* of April 8th, 1899, of a case in Paris, when Madame Moekert had her hip examined by x rays. The first "sitting" lasted forty minutes, the second forty-five minutes, and the third an hour and a quarter. The court decreed that a medical commission

be appointed to decide the duration of the examination considered safe. Two years later the *Lancet* reported the continuation of this case. When it came up for trial, the defence was that the method of application of radiography was not yet formulated, that no one knew the conditions which gave rise to burns in some people and not in others, and that consequently the radiographer was not responsible. The court gave the full amount of damages asked for (5,000 francs) and found that the radiographer had acted imprudently, more like a workman than a medical man, and that his apparatus was defective. The judgement was subject to appeal.

It is interesting nowadays to think of exposures of forty to fifty and seventy-five minutes in order to make a roentgenogram. The dose of x rays which will cause a burn is pretty exactly known now, and, though there may be a slight difference in the reaction of one person compared to another, it is not sufficient to justify a statement that a dose which will have no effect on one person will cause a serious burn on another.

Again, the *London Daily News* of May 1st, 1899, records that in Chicago a patient was awarded 10,000 dollars for injury caused by the x rays. These are the earliest medico-legal cases I have found.

In June, 1901, Mr. Golding Bird wrote in the *British Medical Journal* on the medico-legal aspect of x rays in regard to fractures, and pointed out the necessity of employing an expert to make the roentgenogram and an expert to interpret it. There is no need to dilate on the fact that this advice, given thirty years ago, is as sound to-day. Mr. Golding Bird cites instances in which a skiagram has shown what appeared to be a fracture where none exists, others in which a fracture has been missed altogether, and others again in which, owing to the well-known translucency of young callus to the x rays, it is possible to show a fracture as still existing which has united sufficiently to bear weight, and he arrives at the conclusion that skiagraphy should be employed only as a subsidiary agent in diagnosis, and that even in this secondary capacity its evidence in cases of difficulty and doubt should be received with caution and only after due interpretation by someone whose experience warrants him to speak with authority.

X-ray films can be used to great advantage in medico-legal cases without ever reaching a court. I remember one such case in which a woman fell from a moving street car and claimed compensation for a fractured femur above the knee. She was carried to her home, where she lay for six weeks under the care of a doctor, and was then transferred to the Royal Victoria Hospital, where an x-ray of her knee was made. It showed a fracture above the knee in poor position, and callus was present. I formed the opinion that the fracture was much older than six weeks. Shortly after this, a representative of the street railway company, the claims adjuster, came to see me and said: "We admit the accident and the fracture, and wish to settle for it without going into court." In the interests of justice I felt bound to express my opinion that the street railway company was not responsible, and that the fracture might have happened ten years earlier. The agent was dumbfounded, and asked me what he was to do. I told him to investigate the accidents brought to hospitals in the city for the last twenty years, and look out for the name of the patient. He did so, and at the third hospital he found the name of the woman and the fracture described six and a half years previously. With full information on the case he charged the woman with intent to defraud, and she admitted it and withdrew her claim. The company had been willing to settle for 2,000 dollars.

The occurrence of a pathological fracture, due to negligence of the same street railway company, again brought the same claims adjuster to me, and once more he told me his company admitted responsibility and wished to settle out of court. X rays showed a recent fracture of the femur. The surgeon in charge of the case was surprised when I pointed out that the fracture was a pathological one. The case went to court as an ununited fracture, and it was admitted in court that it was a pathological fracture,

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