THE PATHOLOGY OF INTRACRANIAL TUMOURS.

By DOROTHY S. RUSSELL, M.D. (Lond.).

(Member of Scientific Staff, Medical Research Council. From the Bernhard Baron Institute of Pathology, the London Hospital.)

The following account of the pathology of intracranial tumours must be limited through considerations of space. Attention will therefore be directed chiefly to tumours of neurosurgical importance, the shorter notes on rare kinds being supplemented with bibliographical references for those readers who desire greater detail.

I. Skull.

A. PRIMARY TUMOURS.

Primary tumours of the vault or base of the skull are rare. Cushing (1932) records 14 examples only in his series of 2023 verified cases of intracranial tumours.*

(1) **Osteomata** are composed either of dense ivory or spongy bone. The ivory variety predominates in the skull where it usually protrudes as an exostosis from the inner or outer table or projects into one or more of the air sinuses. Those that involve the ethmoid cells and orbital region are of importance (Cushing, 1927) since they may project into the anterior fossa causing cerebral compression.

(2) **Chondromata and chondrosarcomata** may arise from the bones preformed in cartilage at the base of the skull and project into the middle or posterior fossæ, or both. In two examples of myxochondrosarcoma, examined at the London Hospital, a smooth lobulated mass of brittle, translucent grey tissue projected from the dura into the middle and posterior fossæ of one side, invading or displacing the pituitary body and indenting the adjacent temporal lobe and brain stem. In both death was due to subdural hæmorrhage. In one subject Ollier's disease was also present. Microscopically the tumours are composed of typical and atypical cartilage, the stroma being largely myxomatous and focally calcified.

(3) **Chordoma**, derived from notochordal remnants in the basisphenoid or basioccipital bone, may resemble (2) macroscopically. Microscopically such tumours are composed of alveolar masses of large "physaliphorous" cells of characteristic foamy appearance due to the presence of mucin (Fig. 1. Plate 1), which is also present to a variable extent in the stroma. Glycogen has also been demonstrated in the cells. (See also Burrow & Stewart, 1923-24).

Cholesteatoma, solitary plasmacytoma and cavernous angioma are all very rare tumours of the diploë.

II. Meninges.

(1) **Meningioma** (syn.: *dural endothelioma, arachnoid fibroblastoma, meningeal fibroblastoma*). These are benign, circumscribed tumours usually arising from and firmly attached to the dura, and embedded in but seldom invading the brain. They constitute 14 per cent. of all primary intracranial tumours and are most frequent in the middle and later decades. The regions in which most are found are (a) parasagittal, (b) over the cerebral convexities, especially the frontal region, (c) olfactory groove, (d) sphenoidal ridge, (e) tuberculum sellæ, (f) near the lateral sinuses. The frequent situation of these tumours in the neighbourhood of the arachnoid villi and their histology strongly support the theory that they are of arachnoid origin. The finding of tumours at more remote points, for example over the lateral aspect of the cerebrum, does not nullify this theory since Schmidt (1902) demonstrated isolated nests of arachnoid cells within the dura remote from

* This series includes 4.2 per cent. of secondary tumours, obviously too low a figure because such cases tend to be excluded from any neurosurgical clinic. In addition 2.2 per cent. of cases are listed as "inflammatory tumours" i.e. granulomata. In the following pages Cushing's figures have been adjusted so that the percentages refer to primary intracranial tumours only.

the sinuses. These nests increase in frequency with age. Study of the spinal meningiomata and of certain intraventricular tumours arising from the stroma of the choroid plexuses shows that the pial and arachnoid membranes may also, though more rarely, be the site of origin of these tumours.

The meningioma typically is a firm, ovoid or bun-shaped mass with an encapsulated, irregularly lobulated, or smooth surface traversed by many small veins and capillaries (Fig. 2. Plate 1). Tumours arising from the falx or tentorium may be of dumb-bell shape owing to their growth from either side of the dura. Less frequently the tumour forms a thin layer on the inner surface of the dura ("meningioma-en-plaque") or, more rarely, is villous. The surfaces are usually pinkish-red or grey and when cut are tough and fibrous, with a grained appearance either of whorled character or of streaks radiating fan-wise from the dural attachment. The hæmangeiomatous variety appears highly vascular; the xanthomatous is distinguished by opaque ochreous areas, especially beneath the capsule. The skull at the site of dural attachment often shows a diffuse thickening or "hyperostosis." Both tables may bulge, or the inner table only may show a conical projection. Cushing (1922 (a)) estimates that hyperostoses occur in about 25 per cent. of all meningiomas. It has usually been assumed that this change is accompanied by an invasion of the medullary spaces by tumour. Where the bony thickening is great, as in meningioma-en-plaque, such invasion is microscopically conspicuous (Fig. 3. Plate 1) and may even extend into the temporal muscle. But where the thickening is slight and confined to the inner table the medullary spaces often show merely enlargement and fibrosis. Thickening and invasion of the bone by tumour is frequent in the basal meningiomata. It has been noted in 5 of 8 examples occurring in the anterior fossa at the London Hospital, an observation which suggests that direct trauma plays little part in the production of this bony change, although it seems likely that trauma is an ætiological factor in the production of meningiomas as a class. (Cushing (1922 (b))).

The microscopical appearances of these tumours vary considerably. Bailey and Bucy (1931) recognised nine types. Analysis of 104 surgical specimens at the London Hospital has led to their subdivision into the following groups, arranged in order of frequency: (i) endotheliomatous, 56.6 per cent., (ii) fibroblastic, 29.2 per cent., (iii) angioblastic, 7.5 per cent., (iv) xanthomatous, 3.8 per cent., (v) myxomatous 2.8 per cent. Full histological details are published elsewhere (Bland & Russell, 1938), but the following summaries provide the main points.

- (i) *Endotheliomatous*: alveolar masses or sheets of large polygonal cells often with indefinite borders. Whorls and psammoma bodies often present, sometimes abundant. Fibroglia fibrils absent. Reticulum fibres confined to vessels and trabeculæ. Many transitions between (i) and (ii) (Fig. 4. Plate 1).
- (ii) *Fibroblastic*. Interlacing bundles of long spindle cells containing fibroglia fibrils. Coarse reticulum and collagen fibres often present. Whorls and psammoma bodies scarcer than in (i).
- (iii) *Angioblastic*. Rich network of capillary spaces lined with plump endothelial cells. Similar cells filling tissue between capillaries. Abundant reticulum but no fibroglia fibrils present. Interstitial cells may be xanthomatous.
- (iv) *Xanthomatous*. Like (i) but cells in many areas filled with anisotropic lipid.
- (v) *Myxomatous*. Spindle and stellate cells unevenly distributed in a stroma giving reactions for mucin, and rich in reticulum fibrils. Fibroglial fibrils absent.

Apart from the tendency towards excessive hæmorrhage during operative removal in group (iii) this histological sub-division does not appear to be of much clinical significance. A detailed account of the meningiomas has recently been published by Cushing & Eisenhardt (1938).

(2) **Sarcoma.** Circumscribed and diffuse primary sarcomata of the meninges have been described; they are exceedingly rare. It must be remembered that the term "sarcomatosis" was often used in the older literature for a condition in which the leptomeninges were infiltrated with "small round cells" now known to be of neurogenic origin (See medulloblastoma).

(3) **Melanoma.** The pial cells over the base of the brain, particularly the medulla oblongata, often contain melanin. Benign and malignant melanomata may arise from these cells but are extremely rare. Before claiming that such tumours are primary it is necessary to make an exhaustive autopsy, including an examination of the eyes. *Diffuse melanosis* (Virchow), of the pia is a rare congenital condition associated with pigmented nævi in the skin, and is one of the many causes of congenital hydrocephalus. The areas affected show a diffuse discolouration varying from café-au-lait to brownish-black. Microscopically the leptomeninges are infiltrated with pigmented nævoid cells which infiltrate the adjacent nervous tissue along the sheaths of the perforating vessels. (See review of published cases by Schnitker & Ayer, 1938).

(4) **Lipoma.** These rare tumours, arising in developmental rests, may be found in the mid-line over the corpus callosum, tuber cinereum or mid-brain. Although sometimes deeply embedded in the brain their pial connection is always retained. They rarely cause symptoms (Ewing, 1922). A review of the literature with an account of a case showing extensive lipomatosis of the meninges has recently been published by Baker and Adams (1938).

(5) **Cholesteatoma** (syn.: pearly tumour of Cruveilhier). These epidermoid tumours are also derived from developmental rests, and may arise in the leptomeninges at the base of the brain or in the posterior fossa. They are rare, constituting, with dermoid cysts to which they are closely akin, only 15 in Cushing's series of cases. Externally they are circumscribed and smooth. Their glistening, pearly appearance is due to the accumulation within the tumour of concentric layers of horny and waxy material which have been exfoliated from the epidermal lining. This lining, which microscopically may either be of a simple squamous or prickle-celled character, rests upon a collagenous basement membrane derived from the pia, which forms its outer boundary. These tumours should be distinguished both from the cholesteatomata of the middle ear, which are of a chronic inflammatory nature, and from the cholesteatomata of the choroid plexus, which are degenerative products.

(6) **Gliomatosis.** Rare examples occur, usually in young children, in which the leptomeninges are diffusely infiltrated with glial tumour cells of a polymorphic character and in which no primary tumour can be demonstrated within the brain or retina. The most plausible explanation of such cases is that the tumour has arisen superficially, either in the marginal glia or within an island of neuroglial tissue present as a developmental abnormality within the leptomeninges. Such islands are sometimes met, especially about the brain stem, in the microscopic examination of unselected necropsy material. The importance of making a full examination of the central nervous system must, however, be remembered since an intramedullary glioma of the spinal cord may spread secondarily through the leptomeninges, even reaching the brain (Mallory, 1908; Eden, 1938).

Secondary gliomatosis of the leptomeninges may occur in a wide variety of gliomata of the brain, but especially in medulloblastoma (Cairns & Russell, 1931).

III. Nerve Roots.

Neurofibroma (syn.: *perineurial fibrolastoma*, *neurinoma*). This most commonly occurs as the *solitary acoustic nerve tumour* (Fig. 5. Plate 2) which constitutes 9.3 per cent. of primary intracranial tumours (Cushing). It forms a solid, rarely cystic, encapsulated, lobulated mass occupying the course of the eighth nerve in the cerebello-pontine angle and deeply indenting the adjacent cerebellum and brain stem. It frequently extends, by the internal auditory meatus, into the petrous bone. Opaque yellow xanthomatous areas may be visible to the naked eye, especially beneath the capsule. It is benign and never invades adjacent structures. Microscopically it is composed of interlacing bundles of long spindle cells which sometimes show regimentation of their nuclei or "palisading" (Fig. 6. Plate 2). Whorls are often present but are less definite than in the meningiomata. Psammoma bodies do not occur. Fibroglial fibrils are often demonstrable within the cytoplasm of the cells, but are seldom as conspicuous as in the fibroblastic type of meningioma. Reticulum fibrils, on the other hand, are present between all the cells in well preserved areas with a regularity and richness that is highly distinctive (Fig. 7. Plate 2).

Solitary neurofibroma may also occur, though rarely, on other cranial nerve roots, notably the trigeminal. The Gasserian ganglion is also involved in such instances with the formation of a dumb-bell shaped tumour, the greater part of which is beneath the tentorium (Krayenbühl, 1936).

Multiple neurofibromata characterise the central form of von Recklinghausen's neurofibromatosis. In this disease bilateral acoustic nerve tumours are constantly found while a variety of other nerve roots, both cranial and spinal, are similarly involved. Other tumours, such as meningiomata and gliomata, may also be found in the brain and spinal cord, notably glioma of the optic chiasm. Many authors draw a cytological distinction between the solitary and multiple tumours. Penfield designates the former as perineurial fibroblastoma, the latter as neurofibroma. The perineurial fibroblastoma is characterised by palisading of its nuclei and by its freedom, except at the periphery, from nerve fibres. The neurofibroma, on the other hand, shows a less regular arrangement of its component cells and is traversed by medullated or non-medullated nerve fibres. It is not denied, however, that typical perineurial fibroblastomata are a conspicuous feature in von Recklinghausen's disease (Figs. 6 and 7 being taken from such an example) whether the neurofibromatous type of tissue can be demonstrated or not. The distinction therefore appears to be of academic importance only. The fact that the disease is hereditary suggests that a developmental disturbance of the ectoderm and mesoderm is responsible. Other manifestations are pigmented moles, café-au-lait spots, peripheral neurofibromata and diffuse thickenings of the nerves. It is remarkable that in examples where peripheral tumours are numerous the central nervous system appears free, and *vice versa*.

IV. Blood Vessels.

The blood-vessel tumours as a group compose 2 per cent. of intracranial tumours (Cushing). They may be subdivided as follows:—

1. **Congenital maldevelopments.** This class comprises certain vascular lesions which, although tumour-like, are more correctly termed *hamartomata*, as

defined by Albrecht (1904), from ἀμαρτία, error. The vascular hamartomata to be considered are:—

- (a) Cirroid or serpentine angioma.
- (b) Capillary telangiectasis.
- (c) Cavernous hæmangioma.

(a) The *cirroid or serpentine angioma* is composed of abnormally large and tortuous vessels forming a tangled mass in the leptomeninges and penetrating the underlying brain for a variable distance. The contributing vessels can be recognised and named anatomically. The angioma may be composed of veins alone or of veins and arteries. The latter is also known as arterio-venous aneurysm, an unfortunate term, and characteristically pulsates causing a bruit which can be heard over the skull. Any part of the brain may be involved but the commonest site is in the area supplied by the middle cerebral artery. Venous malformations are sometimes associated with a homolateral port-wine stain or nævus in the skin supplied by the trigeminal nerve, and with congenital glaucoma, or buphthalmus. Likewise, since the vessels in these malformations are apt to become calcified the clinical picture may be completed by the characteristic radiographic appearance to which Parkes Weber (1922-23) first drew attention. Sturge had described a case as early as 1879 in which congenital glaucoma and a port-wine stain were associated with fits referable to the hemisphere of the same side. The radiological contribution completes the clinical syndrome to which the name *Sturge-Weber's disease* is widely given or, in France "syndrome neuro-cutané." The condition is mostly seen in children and is rarely familial. Cobb (1915) observed that a similar venous anomaly of the spinal cord might be associated with a cutaneous vascular nævus in the same segment.

Histologically the arteries and veins composing the lesion are for the most part structurally recognisable as such, but they often undergo hyaline and calcareous degeneration. In addition the muscular portions of their walls are often deformed by irregular hyperplastic foci or leiomyomata. Where the vessels penetrate the brain they are separated by nervous tissue which has undergone gliosis. Macrophages containing iron pigment are often abundant in this tissue.

(b) *Capillary telangiectasis*. This rare lesion is usually a chance finding at necropsy and seldom causes symptoms. The commonest site is in the pons and mid-brain and in this situation rupture has been known to cause death. Telangiectases may be multiple and may also be associated with multiple cutaneous foci (Osler's disease), a combination that tends to be familial (Kufs, 1928). Histologically the area contains a large number of greatly distended capillaries of normal structure separated everywhere by unaltered nervous tissue.

(c) *Cavernous hæmangioma* (syn.: cavernoma). This is closely allied to, and has often been confused with (b). It is rarely met in the brain, the commoner sites being the basal ganglia or subcortical white matter. In the former position they may give rise to internal hydrocephalus, in the latter, from their predilection for the Rolandic area, to Jacksonian epilepsy. Microscopically this lesion is essentially similar to the cavernous hæmangioma of the liver, the walls of the blood spaces being of capillary structure and contiguous except at the periphery where tongues of glia intervene. An important distinguishing feature from (a) is the absence of any large vessels of supply, the adjacent leptomeninges appearing normal except for the presence in some instances of slight rusty pigmentation.

2. *Capillary hæmangioblastoma* (syn.: *Lindau's tumour, angioréticulome*). This is a true tumour capable of growth, invasion and of recurrence after in-

complete removal. It occurs almost exclusively in the cerebellum or medulla oblongata. Some examples are solid and cystic, others entirely solid. On opening a cystic tumour the walls appear everywhere to be composed of smooth neuroglial tissue except at one point where a "mural nodule" of yellowish-red tissue is situated. This nodule may be relatively minute but is nevertheless responsible for the cyst which will not be refilled if the nodule is removed. These tumours are finely spongy, occasionally showing cavernous spaces. Their cut surfaces are frequently ochreous from the presence of large quantities of intracellular lipid.

Microscopically (Fig. 8. Plate 2) the tumour is composed of capillaries of varying calibre lined with rather plump endothelial cells and separated by closely packed polygonal cells many of which are filled with Sudanophil, anisotropic lipid. With suitable silver stains a rich net-work of reticulum is demonstrated constituting the capillary basement membranes and branching between the interstitial cells (Fig. 9. Plate 3). The question of the origin and nature of these interstitial cells has been rather neglected. It is clear that they are neither of neuroglial nor of microglial origin. They are identical in appearance with the cells in many meningiomata, especially the angioblastic and xanthomatous types, and there can be little doubt that they are of pial origin. This view is supported by the fact that many of these cerebellar tumours are obviously contiguous with, and in some instances involve the pia. Tumours that appear to be deeply embedded in the parenchyma may nevertheless show continuity with the pia in the depths of a sulcus. Moreover in some examples of capillary hæmangioblastoma there are cellular, relatively avascular, areas indistinguishable in appearance from the endotheliomatous meningioma. Again, in two cerebellar examples examined at necropsy, pial tumours of identical appearance were also found in the spinal cord. The close resemblance between the capillary hæmangioblastoma and the angioblastic meningioma cannot be dismissed as superficial and the claim of Globus (1937) that "the Lindau tumour is little more than a hemangioendotheliomatous variety of meningioma" seems justifiable.

Nevertheless, even if this is conceded, the Lindau tumour has certain important and distinctive associations, to which the name of *Lindau's syndrome* has been given. In examples of this syndrome, which is often familial, the cerebellar tumour is associated with one or more of the following conditions: angiomatosis retinæ (von Hippel's disease), congenital cysts of the pancreas and kidneys, and benign tumours of the kidneys and suprarenal glands (collectively termed "hypernephroma" by Lindau). Evidence of the syndrome is however confined to a minority of cases exhibiting the cerebellar tumour: it was demonstrated in 2 only of 9 cases that came to necropsy at the London Hospital within recent years. Further details of the blood-vessel tumours of the brain are given in the excellent monographs by Cushing and Bailey (1928) and by Bergstrand, Olivecrona and Tönnis (1936).

V. Brain Proper.

The overwhelming majority of tumours in this class are gliomata, tumours of the neuroglia or supporting tissue of the brain, while those composed of neurones or of neuroblasts are excessively rare. Together they comprise 45.5 per cent. of primary intracranial tumours (Cushing).

I (a) Neuroblastoma. Unless the term is appropriate to the medulloblastomas (see below) it is doubtful whether such tumours are found in the central nervous system. Bailey (1932) states that he has seen three examples but includes

them "for statistical purposes with the medulloblastomas of which they may be considered a variant." None has been identified at the London Hospital.

(b) **Ganglioneuroma.** Tumours containing differentiated, sometimes multinucleate, neurones containing Nissl substance have rarely been met in the frontal and temporal lobes, tuberal region, pineal body and cerebellum. They are usually well defined and are of slow growth. The neurones are separated by somewhat sparse bipolar cells, apparently of glial origin. Calcospherites are usually abundant. While Cushing (1932) quotes only 3 cases, 2 of which were pineal, Globus (1938) has identified "12 cases of ganglioglioma and 10 instances of spongioneuroblastoma" in a group of 178 "supratentorial gliogenous neoplasms" in the Mount Sinai Hospital. From his observations it appears almost certain that many tumours containing neoplastic neurones and neuroblasts have been overlooked. A recent specimen at the London Hospital (S.D. 1023/38), a diffuse subcortical tumour from the right frontal lobe of a man of 25, contained numerous well differentiated neurones containing Nissl substance, separated by abundant plump, occasionally giant, astrocytes, and many less differentiated glial cells resembling astroblasts. Such a tumour appeared to merit the name *ganglioglioma*. Further observations are needed to establish the relationship of such tumours to the gliomata on one hand and the more typical ganglioneuromata on the other.

2. **The gliomas.** The nomenclature introduced by Bailey and Cushing for these tumours (1926) will be followed since this has found the widest acceptance in English-speaking countries. As is well known this classification rests upon the correlation of type cells in different varieties of glioma with morphological stages in the normal development of the neuroglia. Without discussing here either the theoretical basis of such a classification or the possible criticisms that may be levelled against it, it may be stated that it is serviceable in practice and, subject to certain modifications, appears likely to stand the test of time. Lack of space forbids any description of the morphology of embryonic and adult forms of neuroglia. A good account is given by Penfield (1932).

(a) **Medulloepithelioma.** This is a somewhat hypothetical tumour theoretically derived from, and resembling in its structure, the primitive medullary epithelium. A few examples have been described in the pars ciliaris retinae and in relation to the third ventricle. The short account by Bailey and Cushing (1926) of their two examples illustrates the difficulty of diagnosing with certainty so poorly differentiated a tumour. This and Bailey's later admission (1932) that the medulloepitheliomas are often classified with the neuroepitheliomas casts doubt upon the existence of this as a true type of glioma.

(b) **Neuroepithelioma.** This term should be retained for the retinal tumour originally described by Flexner (1891) and for cerebral tumours of similar structure. The retinal tumour, of which a good example has been seen at the London Hospital and described (Cairns & Russell, 1931) is a highly malignant tumour, arising in the rod and cone layer where it forms rosettes composed of a group of cells arranged round a central lumen. The cell margin bordering the lumen is defined by a fenestrated membrane, stainable with phosphotungstic acid hæmatoxylin, through which small blunt cytoplasmic processes protrude in an attempt to form rods and cones. Contrary to what has frequently been stated, blepharoplasts and cilia are not seen in this situation. A certain confusion in the use of the term "rosette" is explained in Fig. 10. Plate 3. Neuroepithelioma of the retina is highly malignant, spreading diffusely through the leptomeninges of the brain and spinal cord. In this

and in the morphology of the cells, apart from rosettes, it resembles medulloblastoma. A strictly comparable tumour of the cerebrum has less certainly been established, but is recognised by Penfield. A possible example is Case 1 of Davie's publication on medulloepithelioma (1932). Many of the other reported cases, including those of Bailey and Cushing (1926) should more properly be regarded as well-differentiated ependymomas in as much as the tumour cells form the rosettes of Bailey and bear blepharoplasts and occasionally cilia along their central borders.

The curious misapprehension has gained currency that the ependyma is ciliated and provided with blepharoplasts during a short period of intra-uterine life only. Actually this is true of the epithelium of the choroid plexuses alone. It is however generally agreed that the primitive medullary epithelium is non-ciliated. As shown by His (1889) cilia begin to appear in the embryo at about the end of the fifth week. My own observations on fresh human material confirm this. In a 7 to 8 weeks embryo cilia were restricted to the low columnar epithelium of the roof-plate and choroid plexuses of the hind brain. At 10—12 weeks cilia were present on the choroid plexuses but not the walls of the lateral ventricles; they were also present in the Sylvian aqueduct and parts of the third ventricle. At 18 weeks fewer cilia were present on the choroid plexuses; they extended over the medial walls of the lateral ventricles but were absent where proliferation of the primitive epithelium was still in progress. Well-formed cilia were present throughout the rest of the ventricular system and in the central canal of the spinal cord. In a foetus of 22 weeks the cilia had almost disappeared from the choroid plexuses but were more wide-spread in the lateral ventricles. They were conspicuous in the third and fourth ventricles and in the central canal of the spinal cord. In a premature infant the appearances were similar except that the choroid plexuses were now free from cilia. The lateral ventricles were well ciliated except over the basal ganglia. In fresh adult material cilia and blepharoplasts can always be demonstrated along the free borders of ependymal cells. They are not, as is often claimed, restricted to a few sites such as the floor of the fourth ventricle and the central canal of the spinal cord.

From the above it appears incontestable that, far from being primitive, the ciliated ependymal cell is the mature, fully differentiated form. It is necessary to insist upon this because it affects our conception both of the neuroepithelioma and of the ependymoma. The former, as described by Bailey and Cushing, is composed of cells arranged in rosettes, bearing blepharoplasts and sometimes cilia along the free borders of their central ends while the other end extends as a process into the surrounding tissue. Such tumours are macroscopically well defined, occupy the neighbourhood of the ventricles and are clinically benign. In no feature do they suggest a primitive type of tumour.

(c) *Ependymoma*. The ependymal tumours are relatively benign and of slow growth. They arise both in children and in adults in relationship to some part of the ventricular system. They are also found in the spinal cord and filum terminale. In some examples the tumour may project into the ventricular cavity, and is then often soft and papillary; in others it forms a circumscribed mass in the adjacent nerve tissue. There is considerable variation in the microscopic appearances, and sub-divisions have been formed accordingly (Kernohan & Kernohan, 1937). Here it may be said briefly that the cells in well-differentiated types tend to form rosettes, the free margin of the cell being occupied by a row of blepharoplasts and, sometimes, cilia. The other end of the cell is prolonged into a process in which neuroglial fibrils can usually be demonstrated (Fig. 11. Plate 3). These processes tend to radiate towards vessels. In some examples this tendency leads to the predominance of perivascular pseudo-rosettes. Such tumours may only be distinguished from astroblastomata by careful examination and, in particular, by

the demonstration of blepharoplasts. A search should be made for these in the best preserved and most cellular parts of the tumour.

When ependymal cells become displaced from their normal position lining a cavity, as in obliteration of the central canal of the spinal cord, they lose their cilia and the blepharoplasts are shifted into a more central position in the cell. They are then demonstrated by phosphotungstic acid hæmatoxylin as a group of minute spherical or rod-shaped bodies occupying a faintly stained area in the cytoplasm near the nucleus. Small isolated groups of such cells are frequently found in normal brains near any fold in the ependyma, for example the horns of the lateral ventricles and the foramina of Luschka.

As originally described by Mallory (1902), whose classical description of these tumours appears to have been somewhat neglected, the ependymomas often contain relatively acellular areas in which neuroglial fibrils are abundant. Such areas may even simulate an astrocytoma (Fig. 12. Plate 3).

(d) *Medulloblastoma* (syn.: *neuroblastoma* (Wright), *neurospongiome* (Roussy and Oberling)). This highly malignant tumour of children and, more rarely, of young adults, appears to be confined to the cerebellum. It arises as an ill-defined, soft, grey, crumbly mass in the vermis or lateral lobes and tends to spread rapidly through the subarachnoid space, especially of the spinal cord. Retrograde metastasis in the ventricles may also take place, a favourite site being the floor of the third ventricle. An apparently authentic instance of metastasis outside the nervous system in an example of medulloblastoma is described by Nelson (1936). Microscopically it is composed of small, closely packed cells with relatively large nuclei, containing a dense net of chromatin and inconspicuous nucleoli. The cytoplasm is scanty and is sometimes drawn out into a short, carrot-shaped process. In some examples such cells are clustered into spheres, their processes being directed towards the centre (the rosettes of Wright (Fig. 13. Plate 4)). Multi-nucleate giant cells are occasionally seen and mitoses are usually abundant. Rarely the cells appear as slender uni- or bipolar spongioblast-like cells the processes of which contain delicate neuroglial fibrils. Differentiation towards neuroblasts has been described by Bailey.

The histogenesis of the medulloblastoma and its relationship to the gliomas as a whole is unsettled. Its virtual confinement to the cerebellum and its obviously embryonic character render attractive the suggestion of Stevenson and Echlin (1934) that it arises in the foetal granular layer of Obersteiner. This subpial layer (Fig. 14. Plate 4) disappears during the first year of extra-uterine life. It is composed of indifferent cells which migrate inwards to form the neurones of the granular layer proper. It is less certain whether they differentiate also into neuroglial cells. Should this hypothesis be correct it would explain many of the observed characteristics of the tumour, including its resemblance to the neuroblastoma of the suprarenal medulla.

(e) *Spongioblastoma polare* (syn.: *neurinoma centrale*). According to Bailey and Eisenhardt (1932), these remarkably benign tumours arise most commonly in the optic chiasm, cerebellum and pons in children and young adults. Macroscopically they resemble the astrocytoma, being relatively well defined and often cystic. Microscopically they are composed of interlacing bundles of long uni- or, more often, bipolar cells the processes of which do not contain neuroglial fibrils although they are described as having both a hard, wire-like appearance and an affinity for gold-chloride-sublimate (Bailey and Cushing, 1926). The resemblance

between these tumours and the piloid variety of astrocytoma (see below) is dismissed as superficial by Bailey and Eisenhardt (loc. cit.). On the other hand tissue-culture experiments have shown that, in two classical examples of "polar spongioblastoma" from the cerebellum and optic nerve respectively, the migrating cells are typical astrocytes (Russell & Bland, 1934). We consider therefore that these two tumours at any rate were astrocytomas. In our view the term polar spongioblastoma might be more suitably applied to a malignant tumour composed of thin, tadpole-shaped cells containing delicate neuroglial fibrils which spreads widely through the leptomeninges (Cairns & Russell, 1931, Case 1). In the case reported the tumour arose in the third ventricle in a girl of 9.

(f) *Astroblastoma*. According to Bailey (Bailey & Bucy, 1930) this is a somewhat rare glioma, chiefly found in the subcortical areas of the cerebrum in young adults. Relatively benign, the average survival period is about 28 months after diagnosis. Macroscopically the tumour is poorly defined and has a greyish cut surface with occasional cysts or areas of necrosis in the central parts. Characteristic examples show a regular arrangement of bulky astroblastic cells in dense rows along the trabeculae and blood vessels of the stroma (Fig. 15. Plate 4). These cells have a few short processes from the head end where the nucleus is situated and a longer angiotropic process ending in a slight expansion or foot. Neuroglial fibrils are rarely found. Many cells are multinucleate but mitotic figures are rare.

(g) *Astrocytoma*. This is one of the commonest types of glioma, and perhaps the most benign. In children it occurs chiefly in the cerebellum and is then often well defined and sometimes cystic. The cerebral examples, on the other hand, are more commonly found in adults and are often diffuse. The pons is a fairly common site of diffuse astrocytoma, giving rise to what is sometimes called "diffuse hypertrophy." Other sites are the mid-brain and optic chiasm.

The astrocytoma varies in its macroscopic appearances. Characteristically it is uniformly smooth and milky-white, the more fibrous examples being exceedingly tough and rubbery. In the cerebellum they are often rather soft or even gelatinous in places; their texture is sometimes spongy from the development of minute cystic spaces through degeneration. Calcified particles are moderately frequent. Although benign they often infiltrate the overlying leptomeninges, especially in the cerebellar examples. Areas of hæmorrhage and necrosis are rarely present.

The microscopic appearances also vary and they have recently been divided by Elvidge, Penfield and Cone (1937) into three groups (1) piloid, (2) gemistocytic and (3) diffuse. Tumours of the *piloid* group, mainly cerebellar examples, are composed of bundles of long slender hair-like cells containing neuroglial fibrils (Fig. 16. Plate 4). Tumours of the other two groups are confined to the cerebrum. The *gemistocytic astrocytoma* (Fig. 17. Plate 5) is macroscopically well defined and is composed of plump cells with bulky cytoplasm and stout neuroglial fibrils which tend to be confined to the periphery of the cell. This type has been named "*astrocytome giganto-cellulaire*" by Roussy and Oberling. *Astrocytoma diffusum* infiltrates and causes great induration of large areas in the cerebral hemispheres; it is composed of relatively small cells which produce an abundant intercellular tangle of neuroglial fibrils (Fig. 18. Plate 5). Included normal elements of the brain undergo little destruction.

(h) *Spongioblastoma multiforme* (syn.: *glioblastoma multiforme*). This is perhaps the commonest type of glioma and one of the most rapidly fatal. It usually occurs in the deep parts of the cerebral hemispheres in adults as an ill-defined

somewhat vascular mass the cut surfaces of which present a variegated appearance. Extensive areas of necrosis, mostly in the central parts, are intermingled with hæmorrhages and small cysts, while the growing margins are composed of greyish-white granular tumour tissue. In many examples tougher greyish-white areas suggestive of astrocytoma can be identified at one extremity of the tumour. The corpus callosum is a favourite site, extension sometimes taking place throughout the greater part of this structure. Again the tumour may extend from the corpus callosum into either corona radiata. Superficial tumours are apt to infiltrate the adjacent leptomeninges, and to become adherent to the dura although they seldom invade it.

Microscopically there is great variation in the appearances both in different examples and in different parts of the same tumour. Variability in cell form is a characteristic feature, many of the cells being undifferentiated polygonal and pyriform cells. Uni- and bipolar "spongioblasts" may form pseudo-rosettes round vessels and palisades along the borders of necrotic foci (Fig. 19. Plate 5). In many examples every transition between these and fully differentiated astrocytes may be identified. Uni- and multi-nucleated giant cells are often present and may form a conspicuous feature (Fig. 20. Plate 5). Mitoses are usually numerous. Degeneration, necrosis and hæmorrhage are characteristic secondary changes; they are often associated with endothelial proliferation in the smaller blood-vessels which become greatly convoluted, forming structures sometimes resembling the renal glomeruli.

The position of this tumour in the glioma series has always been a difficult question. The polymorphism of its cells hardly entitles it to be regarded as an embryonic type, and the explanation of the presence in so many of the tumours of adult forms of neuroglia as a result of differentiation is contrary to general experience in tumour pathology. The polymorphism in spongioblastoma multiforme is far more readily explained as the result of anaplasia and there is, in fact, abundant evidence that many of these tumours are derived from astrocytomas. Space forbids the examination of this evidence here, but it may be summarised under the following heads:—

1. Presence of considerable areas resembling typical astrocytoma in many examples of spongioblastoma multiforme.
2. Presence of anaplastic foci, resembling spongioblastoma multiforme, in otherwise typical astrocytomas with long clinical histories in (a) cerebrum, (b) cerebellum, (c) pons.
3. Consecutive examinations at biopsy and necropsy, separated by considerable intervals of time, demonstrating marked dedifferentiation in tumours primarily astrocytomatous. Similar anaplastic changes have also been observed in two examples of oligodendrogliomas. Cox (1933) reported anaplasia in an example of ependymoma.

(i) *Oligodendroglioma*. This is a rarer glioma occurring in children and young adults. It is relatively benign and of slow growth. It is usually found in the cerebral hemispheres and has frequently been diagnosed radiographically by the characteristic calcified deposits that appear most frequently in its periphery.

Macroscopically it is usually a well defined, firm solid tumour with a greyish-white slightly granular cut surface. Cysts may be present and collections of sand-like, calcified particles are frequent, especially near the periphery.

The microscopic appearances are characteristic, the tissue being composed of closely packed round or polygonal cells with central round nuclei and very

vacuolated cytoplasm (Fig. 21. Plate 6). Groups of these cells are bounded by a well defined vascular and connective-tissue stroma. Mitotic figures and giant cells are sometimes present; in some examples mitoses are numerous. With appropriate silver methods a variable number of the tumour cells can be identified as oligodendroglial cells (Bailey & Bucy, 1929). In some examples, however, the cells remain unimpregnated by any of the metallic methods although oligodendroglial cells in the adjacent brain tissue may be well demonstrated in the same preparation. The reason for this is unknown. With the gold-chloride-sublimate method a variable number of astroblasts and astrocytes are almost always found. Moreover some tumours of this class contain large areas which histologically are indistinguishable from astrocytoma. The relationships between oligodendroglioma and astrocytoma require further investigation.

3. Tumours of the choroid plexus.

(a) *Papilloma*. This is a rare tumour (0.6 per cent. of primary intracranial tumours, Cushing 1932) occurring most frequently in the fourth ventricle in children. Van Wagenen (1930) in an analysis of 45 examples found that 50 per cent. had arisen in the fourth ventricle, 17.3 per cent. in the third and 34.7 per cent. in the lateral ventricles. Almost all of the lateral ventricle examples have been left-sided. Although histologically benign these tumours are apt to be disseminated throughout the meninges through the carriage of groups of cells by the cerebro-spinal fluid.

Macroscopically the tumour is a moderately firm cauliflower-like growth attached to the choroid plexus and distending the ventricle (Fig. 22. Plate 6).

Microscopically it is composed of papillæ coated with a cubical or columnar epithelium resembling the choroidal epithelium and devoid of cilia and blepharoplasts (Fig 23. Plate 6). The stroma is of connective tissue. In this it is distinguished from papillary ependymomas in which the stroma always contains neuroglia.

(b) *Colloid cyst*. This rare tumour, which is globular and from 1 to 2 cm. in diameter, is situated in the anterior end of the velum interpositum where it blocks the foramina of Monro, causing intermittent acute attacks of internal hydrocephalus. Because of its limitation to this part of the ventricular system it has been suggested that this cyst is derived from the *paraphysis*, an outgrowth or pocket of the third ventricle in the dorsal part of the lamina terminalis (McLean, 1936). The paraphysis is vestigial in man but persists in certain fishes.

Histologically these tumours are lined with a ciliated epithelium, identical with the ependyma, which rests upon a collagenous basement membrane continuous with the stroma of the choroid plexuses. The interior of the cyst is filled with thick glairy fluid or solid gelatinous material.

VI. Cerebral Appendages.

1. **Pineal gland.** Tumours of this gland are in general very rare (0.7 per cent. of primary intracranial tumours, Cushing 1932). They occur more frequently in the male than in the female.

(a) *Pinealoma*. This is the commonest type of growth. It usually forms a circumscribed mass of variable size replacing the gland and causing compression of the quadrigeminal plate and internal hydrocephalus. It has also been claimed by Globus & Silbert (1931) that the pinealoma may arise in ectopic pineal tissue either in the mid-brain or cerebellum. Such a tumour has been described in the mid-brain

by Benedek (1936). Certain examples of pinealoma in the male have been associated with pubertas præcox (Horrax & Bailey 1925). The production of this syndrome in such cases is probably due to abnormal stimulation of the hypothalamus rather than to the suppression of a hypothetical pineal internal secretion since certain hypothalamic tumours have also been described in association with pubertas præcox.

Histologically the pinealoma has a characteristic structure. Large spheroidal cells, interpreted as pineal parenchyma cells, with big vesicular nuclei containing 1—4 conspicuous nucleoli, form solid masses separated by trabeculae of connective tissue and blood vessels about which are clustered numerous small lymphocyte-like cells (Fig. 24. Plate 6). It is claimed (Horrax & Bailey) that processes may be demonstrated in the larger cells similar to those that characterise the cells of the normal pineal gland.

(b) *Teratomas* and *ganglioneuromas* of the pineal gland have also been described; they are extremely rare.

2. **Pituitary gland.** Primary tumours of the posterior lobe are virtually unknown.

(a) *Adenomata of the anterior lobe* are common (19.5 per cent. of primary intracranial tumours in Cushing's series) and are of three types according to the character of their cells:—(i) chromophobe (ii) chromophil, subdivided into (a) acidophil and (β) basophil.

(1) *Chromophobe adenoma.* Small adenomata causing no enlargement of the gland and unaccompanied by clinical disturbances are exceedingly common in the adult. Larger adenomata, up to 1.5 cm. in diameter, may also be symptomless. Symptoms are in fact dependent upon compression by larger tumours of the residual anterior lobe, and pressure upon the optic tracts and base of the brain. Such a tumour usually expands the sella turcica and rises, as a round or dome-shaped mass, behind the optic chiasm to occupy the anterior wall of the third ventricle. They are usually rather soft, granular and friable. Hæmorrhages are apt to occur into them.

Although apparently circumscribed, the microscope often shows invasion by groups of tumour cells of the adjacent dura, brain and even the bony wall of the sella. Nevertheless they are clinically benign and very rarely give rise to metastases. The tumour itself is usually composed of acini of closely packed polygonal cells separated by a scanty stroma of collagen and blood vessels. In other examples the structure is papillary, the cells being columnar or even club-shaped and arranged in rows along the vessels. In some tumours all the cells have an agranular cytoplasm. In others some of the cells contain granules that are grey when stained with acid fuchsin-anilin blue; in such tumours there are usually other cells with terra-cotta or orange-red granules, i.e. transitional acidophil cells. Transitional basophil cells have not been met in chromophobe adenomata.

(ii) *Chromophil adenomata.* These are rarer than the chromophobe kind, but are similar in that small symptomless tumours of both acidophil and basophil varieties may occasionally be found in adults.

(a) *Acidophil adenoma.* This seldom grows to the size attained by the chromophobe adenoma. It is associated with gigantism in the growing subject and with acromegaly in the adult. Macroscopically these tumours resemble the chromophobe variety but differ microscopically in being composed of transitional and mature acidophil cells, or of mature acidophil cells only.

(β) *Basophil adenoma*. Large tumours causing symptoms of intracranial pressure have rarely been recorded. An example, unique in that it gave rise to metastases, has been reported by Cohen and Dible (1936). Both in this and in a large number of recorded cases in which the adenoma was minute the patients displayed a syndrome now named after Cushing. This condition, which is commoner in females than in males, is characterised by the development of obesity, cutaneous striæ, plethora, hypertrichosis, vascular hypertension and, less constantly, of glycosuria and osteoporosis. Similar clinical developments may accompany a neoplasm of the suprarenal cortex, or of the thymus. In these, as in the examples where a basophil adenoma is present, the cytoplasm of the basophil cells of the anterior lobe shows a peculiar hyaline change, (Crooke, 1935), which appears to be pathognomonic, of the syndrome. The significance of this change and the mutual relationships of the endocrine glands in connection with Cushing's syndrome are not yet understood.

(b) *Hypophyseal epidermoid tumours* (syn.: *craniopharyngioma*, *suprasellar cyst*, *cyst of Rathke's pouch*). These tumours, which are usually cystic but may be solid, are held to arise from remnants of the craniopharyngeal duct. They constitute about 4.8 per cent. of primary intracranial tumours (Cushing). Though usually suprasellar they may also be intra-sellar or even infra-sellar. Characteristic examples are found in the floor of the third ventricle in young subjects. They may attain a great size, obliterating the cavity of the third ventricle and causing great deformity of the sella turcica. The greater part of the mass is cystic with thin translucent fibrous walls and straw-coloured or brownish fluid contents in which cholesterin crystals are frequently found. The more solid portions of the tumour are tough, with a smooth outer surface, while deposits of calcium or even bone may be encountered on section. Histologically they are lined with a squamous epithelium resting upon a layer of dense collagen. In the more solid portions the epithelium forms broad anastomosing trabeculæ of cells, often with prickly borders. The collagen occupying the interstices between the trabeculæ frequently degenerates with the formation of cysts. In many of these tumours the cells adjacent to the supporting collagen are of the columnar basal type, giving an appearance which has led to the misapplication of the term "adamantinoma" to such tumours. These columnar cells are not ameloblasts although they may superficially resemble them (Sprawson, 1937).

In rare instances these cysts are lined with a columnar ciliated epithelium. Such examples are usually small, intrasellar tumours or are partly intrasellar.

B. SECONDARY TUMOURS.

Lack of space forbids any but the most cursory description of these tumours.

The intracranial cavity may be invaded by tumours of the orbit, nasopharynx, etc. Diffuse invasion of the dura at the base of the brain gives rise to a variety of oculo-motor and trigeminal palsies through involvement of the cranial nerves by growth. The dura beneath the vault may be diffusely permeated with growth when the adjacent bone is the seat of multiple metastases. Such permeation causes a thickening of the dura ("pachymeningitis carcinomatosa") and is frequently complicated by subdural hæmorrhage (Russell & Cairns, 1934). The most frequent sites of the primary tumour in such cases are the lung, prostate and stomach. Discrete metastases may also be encountered in the dura.

Similarly a diffuse carcinomatosis of the leptomeninges may occur but is very rare. Search reveals a discrete metastasis which, by direct spread, has gained

access to the cerebro-spinal pathway either within the ventricular system or at the base of the brain. The distribution of cells throughout the subarachnoid spaces produces an effect resembling meningitis, hence the term "meningitis carcinomatosa." The clinical picture has much in common with that of tuberculous meningitis.

Metastatic foci within the brain may be single or multiple and all parts may be affected. The subcortical white matter is a common site of small deposits. Considering its relatively small size the cerebellum must be regarded as a site of predilection. Although metastases may be derived from almost all possible primary sources the frequency with which they are attributable to carcinoma of the lung or bronchus is particularly noteworthy. Post-mortem examination in such cases may fail to reveal deposits in any other tissues and, unless an exhaustive search is made throughout the lungs, the cerebral focus may be mistaken for the primary tumour. Such a mistake is especially apt to occur when the primary lung tumour is small and has been entirely symptomless.

Secondary growths of the pituitary gland, whether invasive or metastatic, are remarkable in their predilection for the posterior lobe and it is further remarkable that, in such instances, the posterior lobe may be completely destroyed without the development of diabetes insipidus.

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FIG. 1.—Chordoma. H. & E. $\times 265$.

FIG. 2.—Meningioma.

FIG. 3.—Meningioma invading bone. H. & E. $\times 80$

FIG. 4.—Meningioma. H. & E. $\times 129$.

FIG. 5.—Acoustic neurofibroma.

FIG. 6.—Neurofibroma of posterior spinal root in von Recklinghausen's disease. H. & E. $\times 141$.

FIG. 7.—Same as FIG. 6. Laidlaw. $\times 420$.

FIG. 8.—Capillary hæmangioblastoma. P.T.A.H. $\times 231$.

FIG. 9.—Capillary hæmangioblastoma. Laidlaw. $\times 59$.

FIG. 10.—Diagram : rosettes.

FIG. 11.—Ependymoma : a rosette with fibrils in peripheral processes of cells. P.T.A.H. $\times 735$.

FIG. 12.—Ependymoma : fibrillated area. Blepharoplast. P.T.A.H. $\times 375$.

FIG. 13.—Medulloblastoma, showing rosettes of Wright. H. & E. $\times 367$.

FIG. 14.—Cerebellum of new-born infant showing Obersteiner's layer. H. & E. $\times 106$.

FIG. 15.—Astroblastoma. H. & E. $\times 58$.

FIG. 16.—Astrocytoma : piloid type with calcospherites. H. & E. $\times 425$.

FIG. 17.—Astrocytoma : gemistocytic type. H. & E. $\times 250$.

FIG. 18.—Astrocytoma : diffuse type. P.T.A.H. $\times 510$.

FIG. 19.—Spongioblastoma multiforme, showing palisading about area of necrosis. H. & E. $\times 106$.

FIG. 20.—Spongioblastoma multiforme, showing giant cells. H. & E. $\times 258$.

FIG. 21.—Oligodendroglioma. H. & E. $\times 258$.

FIG. 22.—Papilloma of choroid plexus.

FIG. 23.—Papilloma of choroid plexus. H. & E. $\times 75$.

FIG. 24.—Pinealoma. H. & E. $\times 355$.