EVANS' HISTOLOGICAL APPEARANCES OF TUMOURS

VOLUME 2

DAVID J. B. ASHLEY

THIRD EDITION

CHURCHILL LIVINGSTONE

Evans' Histological Appearances of Tumours

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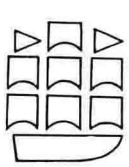

CHURCHILL LIVINGSTONE
EDINBURGH LONDON AND NEW YORK 1978

CHURCHILL LIVINGSTONE
Medical Division of Longman Group Limited

Distributed in the United States of America by Churchill Livingstone Inc., 19 West 44th Street, New York, N.Y. 10036, and by associated companies, branches and representatives throughout the world.

First edition 1956
Second edition 1966
Reprinted 1968
Third edition 1978
Reprinted 1980

ISBN 0 443 01762 X

British Library Cataloguing in Publication Data

Evans, Raymond Winston
Evans' histological appearances of tumours.–3rd ed
1. Tumors
I. Ashley, David James Burrows II. Histological appearances of tumours
616.9'92 PC254 77–30229

Printed in Great Britain by T. and A. Constable Ltd., Edinburgh

Evans' Histological Appearances of Tumours

Preface to the Third Edition

It was a daunting prospect which faced me when I was asked take over the authorship of Dr Winston Evans' book. I was his Senior Registrar in Liverpool and have been in close touch with him over the years, and, because I share his philosophy of the nature of histopathology as a clinical as well as a scientific discipline, I have taken on the task of producing a third edition of what has become a standard work.

The whole of the text has been revised and in large part rewritten to include more recent original work in the field of tumour pathology and a number of new illustrations have been added. In particular the chapter on lymphoid tumours has been extensively revised. Some rearrangement has been necessary, tumours of the endothelium are now included with respiratory tumours rather than among tumours of vasoformative tissue, and the carcinoid and chromaffin tumours are now placed with other tumours of endocrine organs. A separate section on the teratomas has been added because of the unusual nature of these neoplasms and the unusual features of their histogenesis. A major alteration has been to add an introduction and to divide the work into sections each comprising a group of chapters on related tumours preceded by a short general essay on the group as a whole. As in the previous editions the relationship between the clinical and pathological features of the tumours is stressed. I have followed Dr Evans in aiming to produce a work which will be helpful to the practising histopathologist and to his clinical colleagues in their daily work as well as to the trainee and to the research worker.

I am indebted to my clinical colleagues who have allowed me to use data from their patients, and to many colleagues in pathology who have given me slides for illustrations. My thanks are particularly due to Dr Joan Summerell, who has discussed many aspects of the work with me.

Mrs Winston Evans has allowed me free access to the material which Dr Evans had collected in preparation for this edition.

I thank Mr Howard Fry, Mrs Linda Easton, Mr Jeffery Hole and Miss Caroline Penry, who prepared the histological specimens for me; and Mr Hole also carried out a great deal of the photographic work.

Miss Marilyn Marks, librarian to the Swansea Hospitals, helped greatly by collecting and checking many references for me.

I am particularly indebted to my research assistant Mrs Molly Rees B.A., who has typed and re-typed the manuscript, collated apparently innumerable references and has helped with the index.

During the preparation of this work I have held a research grant firstly from the Welsh Hospital Board and latterly from the Welsh Office. I am greatly indebted to them for this help.

My new publishers, Messrs Churchill Livingstone, have given me full cooperation in the preparation of the manuscript and in the editorial work necessary between the stages of typescript and print.

Swansea

DAVID J. B. ASHLEY

Extracts from the Prefaces to the First and Second Editions

'Without some knowledge of the development of the part, it is impossible to arrive at a full understanding of its disease.'

NICHOLSON.

This book is concerned not only with the histological and histogenetical aspects of tumours but also with the development of the tissues and organs from which they arise; it describes the morphology of tumours and seeks also to present certain features of their behaviour and clinical effects which, it is hoped, will be of interest to surgeon and physician as well as of assistance to the hospital pathologist. Toward this end biochemical, haematological and endocrinological features are discussed when they are considered useful in the investigation, diagnosis and prognosis of neoplastic disease. The writer has sought to provide also some information touching upon the incidence of neoplasms, their distribution and their relationship to age and sex.

The spread and mode of origin of tumours is mentioned in some detail and the possibilities of correlating the structure with the behaviour of neoplasms is outlined. In this connection it cannot be emphasized too strongly that it is sometimes impossible to express an opinion with regard to the probable behaviour of a tumour from a study of its histological characters alone, and the careful pathologist will guard against coming to a conclusion until he has not only employed every technical procedure likely to be of value but has also studied in full the clinical features of the case; for it is well known that certain growths, despite the exhibition by them of structural characters usually displayed only by malignant lesions, do not behave as such; there are other growths, apparently of well-differentiated structure, which nevertheless disseminate wildly to all parts of the body.

It is hoped that a sufficient number of illustrations of both rare and common tumours have been included so that reference to original articles for photomicrographs, which is often irksome and time consuming, is obviated; for it is always pleasing to be able to turn up an illustration when discussing a particular tumour with a clinical colleague, and to some extent the book is designed to meet this need in one volume.

The problems of classification and theories of histogenesis are presented, as so often these are relevant to the interpretation of the histological features of neoplasms, and because his views concerning the genesis of tumours are demanded frequently of the pathologist by his clinical colleagues—and also of the student by his examiners. As the understanding of histogenetical problems often can be achieved only by consideration of the normal development of tissues and organs, certain aspects of normal histogenesis, embryology and structure are presented and discussed where this seems to be of particular interest or is thought to be helpful in stressing the similarities and evaluating the differences that exist between normal and abnormal tissue reactions—especially between hyperplastic and neoplastic processes.

The number of cases and specimens available for study by any one pathologist is limited, and it is necessary therefore to correlate one's own experience with that of others; to a large extent this can be carried out only by the gathering of a sufficient number of authoritative articles and treatises from the vast literature that deals wiith neoplastic disease. In this connection the references given at the end of each chapter direct attention only to those articles and books which were consulted by the author specifically for the compilation of the text. The post-graduate student bent upon writing a 'paper' eagerly seeks lists of relevant articles, and it is hoped that among the references given in this book there will be found a sufficiency of old and new ones to meet the requirements of the would-be author.

The material used in the compilation of this book was collected almost entirely at the David Lewis Northern Hospital, Liverpool, and it is with the greatest pleasure that the author acknowledges the assistance given and interest shown by the surgeons and physicians of this hospital—Mr J. B. Oldham, V.R.D., Q.H.S., Mr P. R. Hawe, T.D., Sir Arthur Gemmell, M.C., T.D., Mr E. N. Wardle, Mr W. R. Hunter, Mr W. M. Beattie, Mr G. E. Thomas, Dr C. A. Clarke, Dr A. Thelwall Jones, Dr W. H. R. Cook, the late Professor T. P. McMurray, C.B.E., the late Mr G. E. Simpson, O.B.E., T.D., the late Dr H. S. Pemberton and the late Dr L. Cunningham—their initials appear after the serial numbers of the illustrations of material from the cases which were under their care. Particular thanks are due to Mr Philip Hawe, who read some of the manuscript and gave me much encouragement.

Slides and specimens were also supplied by friends not on the staff of the David Lewis Northern Hospital and the names of these surgeons and pathologists appear after the appropriate legends.

Dr E. K. Dawson of the University Department of Pathology, Edinburgh, read and criticized the whole of the manuscript; for her guidance and encouragement, which were of the greatest help in the preparation of this book, the author is extremely grateful. The writer is also indebted to Dr Dawson for the loan of several slides including those of a tubular adenoma of the testis and of tumours of the urachus.

The first essential for a good photomicrograph is a good section, and any excellence that may be attributed to the illustrations in this book is largely the result of the careful work carried out by Miss Catherine D. M. McDougall, A.I.M.L.T., whose remarkable skill in histology has been of inestimable value and whose photostatic memory has proved often more useful than a filing system. In addition to producing thousands of sections needed for special study and for the composition of the illustrations she has devoted many hours to the preparation of the photomicrographs and to checking the figures and their legends.

To Miss Olive Jones, secretary of the pathology department, the author expresses his unqualified appreciation for the tireless patience with which she has typed and re-typed the manuscript several times. She was invaluable also in collecting and assembling details of the patients' histories and in typing the index; in the former task she received much assistance from Miss

Marjorie Mowat. In the final stages of the manuscript Miss Sheila Manning kindly helped with the typing.

All the diagrams were drawn by Miss Gwenllian Thomas, and it is a pleasure for the author to record his thanks to her.

The task of collecting and checking many references was facilitated greatly by the generous assistance given by Mr and Mrs W. A. Lee of the Liverpool Medical Institution and by Miss Marjorie Conway of the Harold Cohen Library of Liverpool University.

I want to express my especial gratitude to my wife, Margaret, not only for her assistance with the preparation and the correction of the manuscript but also for her invaluable translations of many articles in French and German.

To my publishers, Messrs E. & S. Livingstone Ltd., I am greatly indebted for their co-operation, enthusiasm, and courtesy; no author could wish for greater consideration than was given by them.

THE preface to the first edition pertains to the second except for the addition of twelve new chapters. These have been added for the sake of completeness with respect to neoplasms arising in all organs of the body and relate to aesthesioneurocytomas and tumours of the central nervous system and of the female genital tract and placenta.

Although intrinsic tumours of the brain and spinal cord are not considered so esoteric as to be of little interest to the general pathologist, the writer still regards them as belonging more properly to the special field of the neuropathologist. Tumours of the female generative tract (ovarian neoplasms especially) are treated more extensively.

All the original chapters have been rewritten and enlarged to include newly recognized tumours and their variants. The scope of the present book has changed also inasmuch as the physiological, endocrine, clinical effects and genetic aspects of neoplasms are discussed in greater detail than in the first edition. The results of electron microscopy studies are mentioned only when they bear upon the nature and histogenesis of neoplasms.

Liverpool 1956, 1966 R. WINSTON EVANS

Section 5 Tumours of the Nervous System

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This section is concerned with tumours arising in the central nervous system, its covering membrane, the peripheral nerves and the pineal gland. Because of the development of the specialities of medicine and surgery, neurology and neurosurgery, the majority of patients in whom these tumours are diagnosed are treated in hospitals specializing in these particular diseases, although from time to time patients with brain tumours die suddenly and come to autopsy or are found to have unsuspected tumours of the central nervous system, and so come to the attention of the general pathologist. Tumours of the nervous system are not common. In England and Wales less than one death in 200 is attributable to these lesions (Registrar General, 1971). 1·5 per cent of tumour deaths are due to brain tumours (Registrar General) and in the Birmingham Tumour Registry only 2 per cent of tumours are identified as in this situation (Waterhouse *et al.*, 1970).

The nervous system is an ectodermal structure and arises from the neural plate on the dorsal surface of the embryo. This descends into the mesoderm firstly forming a neural groove and later a neural tube. At the angle between the neural tube and the surface ectoderm a neural crest is formed on either side and from this are derived the cranial and extracranial ganglia and the peripheral nerves. The neural epithelium differentiates in two major directions to form all nerve cells throughout the body and the supporting tissue, the glia, which surrounds nerve cells within the central nervous system. The sensory part of the eye, the retina, is a highly specialized outgrowth of the central nervous system which forms on the end of the developing optic nerve. The refracting parts of the eye develop in the mesoderm and surface ectoderm in response to stimuli from the developing retinal cup. The membranes covering the brain arise from two germ layers, the pia-arachnoid, the two thin membranes closely applied to the brain are derived from neural crest cells, and the thick protective dura is a condensation of mesenchyme which comes to surround the developing brain. The peripheral nerves are surrounded by a sheath of supporting cells, the nerve sheath, which is regarded as being mainly of neural crest origin, although it is possible that some part of the connective tissue sheath may arise from the mesoderm. The pineal gland, the subject of Chapter 5.4 in this section, arises as an evagination of the roof of the primitive third ventricle which as the brain assumes its final form comes to lie posteriorly and inferiorly.

A striking feature of tumours of the brain and spinal cord is that blood-borne or lymphatic metastasis is exceedingly rare. Dissemination of tumour to other parts of the nervous system through the cerebrospinal fluid is seen particularly in the less well-differentiated tumours, but extracranial deposits are almost never seen.

The frequency of the various types of central nervous tumour is markedly unequal. Rubinstein (1972) records that 55 per cent of intracranial tumours can be classified as glioblastoma, 20 per cent as astrocytoma, 6 per cent as ependymoma, 6 per cent as medulloblastoma and 5 per cent as oligodendroglioma. In surgical material, however, the frequency of glioblastoma is somewhat lower than this and a majority of tumours are classifiable as one or other of the grades of astrocytoma. The spinal cord, the caudal extension of the nervous system, is much less commonly affected by neoplasms than is the brain. In my own experience space-occupying lesions in the spinal canal are in a large majority of cases protrusions of the intervertebral disc. Among true tumours secondary deposits from primary tumours elsewhere in the body account for 26 per cent of cases; meningiomas arising from the surrounding membranes 22 per cent; nerve sheath tumours arising from the nerve sheaths within the spinal canal 15 per cent; and a miscellany of bone tumours, lymphoid tumours, developmental cysts and angiomas most of the remainder of neoplasms in this situation. Gliomas arising in the spinal cord are in my experience quite rare.

Central Nervous Tumours in Children

In paediatric practice tumours of the central nervous system occupy a much larger place than they do in adult medicine. Between birth and the age of 9 years 30 per cent of recorded tumours arise in the nervous system and in the following two decades between 10 and 12 per cent (Waterhouse *et al.*), while 16 per cent of tumour deaths in children under the age of 10, and 9 per cent of tumour deaths in individuals between the ages of 10 and 30 are due to tumours of the central nervous system (Registrar General). The frequency and location of nervous system tumours in children differs from that in adults. In adults the majority of tumours arise above the tentorium, while in children 70 per cent of intracranial tumours arise in the posterior fossa. The histological type of tumours is also different in children. Thirty per cent of tumours are in the groups medulloblastoma and medullo-epithelioma, 30 per cent are poorly differentiated astrocytomas and 27 per cent are well-differentiated astrocytomas which often are cystic in type and have only a small nubbin of apparent tumour at one side of the cyst (Willis, 1962).

GEOGRAPHICAL DISTRIBUTION The recorded frequency of nervous-system tumours differs in different parts of the world by a factor of almost 10. In all probability some part of this difference is related to differences in medical practice and in particular to the availability of facilities for extensive investigation of nervous-system disease. Among countries in which medical facilities are well developed there is an appreciably higher frequency of brain tumours in Israel and a low frequency in Japan, among the Japanese of Hawaii, and in India and the West Indies (Doll *et al.*, 1970). The reason for these differences is obscure.

REFERENCES

DOLL, R., MUIR, C. S. & WATERHOUSE, J. A. H. (1970) *Cancer Incidence in Five Continents*. Vol. II. U.I.C.C. Berlin: Springer-Verlag.

REGISTRAR GENERAL (1971) *Statistical Review of England and Wales for the Year 1969* Part II. Tables Medical. London: H.M.S.O.

RUBINSTEIN, L. J. (1972) Tumors of the central nervous system. *Atlas of Tumor Pathology*, Second Series. Fascicle 6. Washington, D.C.: A.F.I.P.

WATERHOUSE, J. A. H., LEVI, J. M. & POWELL, J. (1970) Cancer incidence in U.K. Birmingham Region 1963–1966. In *U.I.C.C. Cancer Incidence in Five Continents*, eds. DOLL, R., MUIR, C. S. & WATERHOUSE, J. A. H. Vol. II. U.I.C.C. Berlin: Springer-Verlag.

WILLIS, R. A. (1962) *The Pathology of the Tumours of Children*. Edinburgh: Oliver & Boyd.

5.1 *Tumours of the Neuraxis*

Neuroglia

Macroglial elements, like astroglia and oligodendroglia, together with the epithelial ependymal cells constitute the three basic glial elements of the central nervous system. Astrocytes predominate in the grey matter, whereas oligodendrocytes, which form the satellite cells of neurons and the interfascicular supporting cells of central nerve fibres, are as numerous in the grey as in the white matter, where they are arranged in rows.

Typical astrocytes are stellate cells with elaborate branching processes, a small body and an oval nucleus of pale and dusty complexion; they are of two varieties: protoplasmic and fibrillary. Protoplasmic astrocytes are characterized by a more abundant granular cytoplasm extending into many complicated, rather thick irregular plasmatic processes. Fibrillary astrocytes contain fine fibrils in their cytoplasm and have fewer but longer, thinner, straighter and less branched prolongations. These two forms, however, are not fixed types since protoplasmic astrocytes can transform into fibrillary or plasmato-fibrillary variants. A special feature of astrocytes is their relation to blood vessels and septa; some of their cytoplasmic processes form podic expansions closely applied to the walls of capillary blood vessels. Indeed, according to Cooper (1935), these plasmatic footplates are not only directed towards a blood vessel wall but appear also to penetrate the perivascular sheath and to encircle the endothelial cells. By means of cytoplasmic processes or glial fibres astrocytes establish an intimate relationship also with other glial cells and myelin sheaths.

As a result either of a reactive or neoplastic response, the cytoplasm of astrocytes sometimes becomes markedly swollen and deeply eosinophilic, and the plasmatic processes thickened and shortened. Cells altered in this way are called 'gemästete', gemistocytic or stuffed astrocytes. Another form of astrocyte is the 'piloid' astrocyte, so called by Penfield (1924). This is an elongated cell which tends to deposit long, hair-like fibrils arranged in parallel sheaves.

Oligodendrocytes were first identified and named by Rio-Hortega (1932); their existence was confirmed by Penfield. These elements vary in size but contain smaller, regular, more rounded and compact nuclei than astrocytes; they have no special relation, or 'sucker' feet attached, to blood vessels and their processes are fewer, less elaborate and more difficult to demonstrate by the metallic impregnation techniques of Cajal and Rio-Hortega than those of astrocytes. In haematoxylin and eosin preparations oligodendrocytes, since they possess clear perinuclear zones, appear as empty cells bordered by a very narrow rim of cytoplasm. Despite these morphological differences oligodendrocytes and astrocytes are probably closely related and are sometimes accompanied by apparent transitional oligo-astrocytic forms (Kwan and Alpers, 1931). Because of their intimate relation to nerve fibres oligodendrocytes may be regarded as the central equivalents of Schwann cells.

Fully differentiated ependymal cells constitute the columnar or cuboidal ciliated epithelium that lines the ventricles of the brain and central canal of the spinal cord. In a modified non-ciliated form this epithelium is continued to cover the vascular tufts of the choroid plexus. Electron microscopy, however, has shown that choroid plexus epithelium also possesses both cilia and microvilli (Luse, 1960). When dislodged from their lining position ependymal cells tend to grow in groups around a central cavity or else in irregular solid clusters (Russell and Rubinstein, 1963).

From the bases of ependymal cells fine processes extend into the medullary substance to form a subependymal fibrillary glial network capable of considerable proliferative activity. In this sub-ependymal zone there are astrocytes of similar cytoplasmic and nuclear structure as ependymal cells, but such resemblances do not necessarily signify that astrocytes are derived from ependymal cells.

With the probable exception of microglia, neuroglia is a product of neuro-ectoderm. The elements that line the embryonic neural tube comprise the germinal layer (medullary epithelium) from which cells migrate and differentiate into two categories: embryonic nerve cells, or neuroblasts, and spongioblasts, or embryonic neuroglial cells. The cells of the germinal layer that remain *in situ* form the ependymal epithelium. The spongioblast is a fusiform cell from one or both poles of which a wisp of cytoplasm is continued as a process that shows no attachment to either a blood vessel or connective tissue septum. The terms 'medulloblast' and 'retinoblast' were introduced to indicate undifferentiated cells in the neuraxis and retina respectively. But there is no clear evidence that the largely hypothetical medulloblast is capable of both neuroglial and neuronic differentiations.

Microglia (Rio-Hortega, 1932), the fourth basic glial element of the central nervous system, is probably of mesodermal derivation, and its cells, which develop from indifferent reticulum cells about the blood vessels, function as macrophages. Microglial cells seldom give rise to neoplasms, though very rare single or multiple tumours (microgliomatosis or primary reticulosis of the central nervous system) that develop usually in the cerebrum of adults have been attributed to such cells (Losli, 1956; Miller and Ramsden, 1963; Russell and Rubinstein, 1963). Such lesions, despite certain histological features in common, belong to a broad group of tumours with many transitional forms. Many are probably primary lymphomas of the central nervous system.

Classification of Gliomas

Assuming the existence of as many types of tumours as there are recognizable forms of mature and immature cells in the developing nervous system, Bailey and Cushing (1926) classified gliomas in terms of normal histogenesis. The classification they advocated was at once widely accepted and has since influenced greatly the nomenclature of primary neoplasms of the brain and spinal cord. Yet it is now questionable whether much is gained by grouping gliomas into the numerous and complex categories such an embryological approach involves. Embryological concepts introduced into such a scheme are often hypothetical and, in as much as many gliomas contain cells that bear no resemblance to those present during the developmental phases

of the central nervous system (CNS), largely inapposite. Certainly the notion that neoplasia implies the de-differentiation of adult type cells into embryonic forms is debatable. Some gliomas, like medulloblastoma, are probably embryonic neoplasms, but others, which are typically tumours of adults, contain a variety of cells that cannot be explained on the basis of the recapitulation by the tumour cells of the morphological characteristics of elements normally seen only in the wall of the early embryonic tube.

This group of tumours exhibits a wide range of structural diversity. Many gliomas, composed of different forms of glial cells, appear to be 'mixed tumours' *ab initio* and the microscopical examination of different sections taken from one such neoplasm often reveals much variation in the type of cell that prevails and from which the tumour acquires its distinctive name. Classification of any one neoplasm, therefore, can be valid only if sampling has been extensive, a process not always applicable to biopsy specimens.

Such a structural variation suggests that more than a single kind of neuroglial cell participates in the formation of a glioma. Indeed, experimental evidence indicates that many if not all gliomas originate because of the neoplastic transformation and proliferation of several different types of neuroglial cells. After stimulation of a region of an animal's brain by a suitable chemical carcinogen various different and morphologically distinct types of glial elements proliferate, almost simultaneously, to form an 'impure mixed cell glioma' (Zimmerman, 1945). Thereafter, multiple 'pure-cell gliomas' can be obtained by the judicious selection of explants from the artificially induced 'mixed' tumour and their subsequent subcutaneous transplantation into homologous animal species.

Certain gliomas tend to arise at definite apparently particular sites in the brain and spinal cord, and this propensity is somewhat useful both in classification and predicting prognosis, a major reason for classifying neoplasms. Such an anatomical predilection is shown also in the case of experimentally produced gliomas (Zimmerman). Carcinogenic pellets placed in contact with ependyma result in the appearance of differentiated or undifferentiated ependymomas; similar pellets implanted into the subcortical white matter often induce a glioblastoma multiforme and, far less frequently, an astrocytoma; carcinogens inserted into the occipital lobe tend to evoke an oligodendroglioma and those introduced into the cerebellum excite usually the formation of medulloblastomas. The proneness of certain morphologically distinctive gliomas to develop in specific regions in the brain, however, is capricious and only of limited value in identification and classification.

The vexed question of classifying gliomas is complicated also by controversial issues, resulting in the creation of varieties and sub-varieties, and the ensuing profusion of synonyms. The problem is not readily resolved since, in this group of tumours, the taxonomic demand that in sound categorizations the various subdivisions must exclude each other, cannot easily be fulfilled. There are so many morphologically mixed and intermediate forms of glioma that often any decision as to what constitutes a difference between separate types of tumour is not only difficult but based entirely on arbitrary considerations. One relies chiefly on the emergence of a histological picture which, though not necessarily specific in the histogenetic sense, allows the recognition of a type of glioma because of the development of a predominating cell, texture, characteristic cellular dispositions or cytological pleomorphism, and these features may be influenced by such considerations as vascular changes, haemorrhage, necrosis, calcification and site of origin of the tumour. The histological appearances of gliomas, however, may be as much induced by the architecture of the adjacent tissues they invade as they are determined by the intrinsic growth habits of the tumour (Scherer, 1938). Indeed, experience has shown that the less complicated the system of classification the more useful its worth and the greater its adaptability and reliability. The tendency therefore is towards simplification of categories (Cox, 1953; Earle *et al.*, 1957; Kernohan *et al.*, 1937; Kernohan and Sayre, 1952; Penfield, 1931; Ringertz, 1950; Helen Russell, 1941; Willis, 1960) and the avoidance of the error of classifying gliomas too exculsively in terms of cytological aberrations of little value in predicting biological behaviour. In fact, Raimondi *et al.* (1962) as a result of their electron microscopic study of brain tumours, are inclined to speak of benign and malignant gliomas rather than astrocytomas, glioblastomas, oligodendrogliomas, etc.

The classification adopted in this chapter is as follows:

(*a*) Astrocytoma group.
(*b*) Oligodendroglioma.
(*c*) Ependymoma and choroid plexus papilloma.
(*d*) Medulloblastoma.
(*e*) Medullo-epithelioma.
(*f*) Neuroblastoma-ganglioglioma.

Such a scheme is elastic and allows for the arbitrary placing of transitional and 'mixed' tumours in more than one group; yet it retains some specificity for tumours possessing a degree of distinctiveness in morphology and location. The term 'blastoma' is devoid of histogenetical implication; with certain exceptions it serves mainly to emphasize lack of differentiation in malignant tumours derived from mature adult tissues.

Three special types of tumour are considered separately. Two of these, the retinoblastoma and the olfactory neuroblastoma were placed in separate chapters in the previous edition and the third, optic-nerve glioma, shows differences of histological and clinical features which demand separate consideration. All three are derived from cells of CNS origin and therefore are best considered in this group.

GENERAL CONSIDERATIONS Gliomas are tumours of the neuroectodermic tissue of the brain and spinal cord; they develop in males somewhat more commonly than in females and, like meningiomas, are not infrequently apparently related in their clinical evolution to trauma. There is, however, no conclusive evidence that such a causal relationship exists. Though but occasionally recorded, the familial occurrence, especially of the same morphological type of glioma, suggests the possible action of genetically dominated factors in the aetiology of certain kinds of tumours of the central nervous system, and Kjellin *et al.* (1960) have described seven families in which gliomas arose in two or more members. Within six of these families the tumours were identical, malignant gliomas in three and astrocytoma, pinealoma and medulloblastoma respectively in the remainder.

Gliomas constitute about 50 per cent of all intracranial neoplasms, and a striking feature is the high incidence in children and adolescents of medulloblastoma and cerebellar astrocytoma, tumefactions which seldom develop during adult life. The common gliomas of adults are cerebral astrocytoma and glioblastoma multiforme and these growths tend to occur in the

fifth decade. Congenital gliomas are extremely rare, only a few cases have been reported (Ashley, 1961; Fuste *et al.*, 1967). The histology of such lesions is variable and may be oligodendrogliomatous, ependymomatous or of astrocytic type.

Gliomas of the spinal cord are uncommon. Their incidence has been variously assessed as 10 to 20 per cent of all tumours of the cord (Amako and Ogawa, 1958; Shenkin and Alpers, 1944) and they arise predominantly in adults. Ependymoma is the common variant (astrocytoma is less frequent) (Anderson, 1966), and the lesions may be associated with a pre-existing syringomyelia (Kernohan and Sayre, 1952). The brain stem is a more infrequent site of origin of gliomas which, in this location, arise more often in children than adults. In the optic nerves and chiasma gliomas develop rarely, but predominantly (75 per cent according to Matson, 1958) in children.

Accounts of ectopic gliomas arising from heterotopic islands of neuroglial tissue in the meninges have been given by Cooper *et al.* (1951) (intraspinal ependymomas and astrocytoma) and Abbott and Glass (1955) (extracerebral astrocytoma). Ectopic gliomatous tumours occur also entirely outside the confines of the craniospinal space, especially in the region of the bridge of the nose (Morley and Cross, 1958), and nasopharynx (Bratton and Robinson, 1946). Such congenital gliomas may be regarded as hamartomatous developments of heterotopic neuro-ectodermal tissue with only a limited capacity for differentiation. Extraspinal gliomas, mainly ependymomas, occasionally arise in the sacral region where they may be associated with spina bifida (Cooper *et al.*).

Gliomas ordinarily form solitary lesions, but multiple tumours of multifocal origin develop in the cerebrum in about 10 per cent of cases of glioblastoma multiforme and 6 per cent of cases of astrocytoma (Courville, 1936). The two tumours may be of differing types (Bastian and Parker, 1970). Gliomas grow expansively; many are also infiltrative and directly destructive. A most common method of spread is by invasion into the subarachnoid space to involve the meninges locally or diffusely (meningeal gliomatosis). Rarely a malignant glioma may spread through the otherwise intact dura (Sanerkin, 1962) and deposits of medulloblastoma have been seen in the skull bones (Corrin and Meadows, 1967). Medulloblastoma, glioblastoma multiforme and ependymoma frequently, and oligodendroglioma occasionally (Blumenfeld and Gardner, 1945), 'seed' along the cerebrospinal axis, and it seems that in certain circumstances most gliomas can produce metastases, limited to the central nervous system, as a result of dissemination via the cerebrospinal channels (Cairns and Russell, 1931). Such tumours are commonly of a less well-differentiated type (Eade and Urich, 1971). It has been shown that there is proliferation of capillary endothelial cells and of fibroblasts in the arachnoid when it is encroached upon by gliomata and it is suggested that this reaction may reduce the possibility of spread of tumours through the CSF (Enestrom 1966). Recurrence of a glioma in or its extension into the scalp through an operative wound in the skull is an occasional complication of craniotomy (Feigin and Volk, 1951; Martin, 1931; Meredith and Sahyoun, 1951), and it is assumed that this is a result of the implantation of tumour cells at the time of operation.

No matter how malignant the histological appearances of the primary tumour, one of the most curious and as yet ill-understood features of gliomas is their inability to produce extracranial secondary growths. Nevertheless, the literature contains many records of gliomas that ostensibly have given rise to metastases outside the limits of the craniospinal bone cavity: oligodendroglioma (James and Pagel, 1951); cellular glioma, possibly ependymoma (Perry, 1957); ependymoma (Cross and Cooper, 1952; Fragoyannis and Yalcin, 1966; Maass, 1954; Patterson *et al.*, 1961; Sherbaniuk and Shnitka, 1956; Weiss, 1955); glioblastoma (Davis, 1928; Ehrenreich and Devlin, 1958; Garret, 1958; Giok and Schoot, 1959; Ley *et al.*, 1961; Smith *et al.*, 1969; Wisiol, 1962); and medulloblastoma (Lewis *et al.*, 1973; Nelson, 1936; Oberman *et al.*, 1963; Paterson, 1961; Rubinstein, 1956). The authenticity of many such reports has been questioned on the grounds of insufficient histopathological data and the failure to exclude the possibility either of the simultaneous coexistence of two independent tumours, one intracranial the other extracranial, or that the brain tumour was a metastasis from a parent neoplasm situated outside the confines of the neuraxis. Indeed, Weiss (1955) enumerated four criteria to be fulfilled before a case is acceptable as a true instance of metastatic spread of an intracranial tumour to extracranial locations. He emphasized: (1) the presence of a single histologically characteristic tumour of the central nervous system, (2) a clinical history indicating unequivocally that the initial symptoms were caused by such a growth, (3) the exclusion of a possible additional primary tumour by a complete autopsy, and (4) a significant correspondence of the histological features of the distant metastases to those of the primary neoplasm in the CNS. Among cases fulfilling these criteria may be mentioned those recorded by Giok and Schoot; James and Pagel; Ley *et al.*; Paterson; Perry; Rubinstein; Sherbaniuk and Shnitka; and Weiss. The metastases have been found in cervical lymph nodes, lung, liver and skeletal tissue.

It appears that most valid instances of extracranial metastatic dissemination of gliomas share one or more of the following features: (*a*) multiple craniotomies possibly allowing the intravasation of neoplastic cells into vascular channels disrupted by surgery; (*b*) direct infiltration of the extraneural tissues by the primary growth at or near the operation site; (*c*) prolonged survival of the patient; and (*d*) post-operative radiation.

Why gliomas fail to metastasize outside the confines of the craniospinal space remains an enigma. Absence of true lymphatics in the central nervous system, the generally short duration of the disease and the failure of gliomas to induce a supportive fibrovascular stroma in tissues other than brain and eye (Greene, 1951) are among reasons generally advanced in explanation of this curious phenomenon. A more important factor is the apparent inability of these tumours to penetrate the dura and extend into the lumina of sinuses and blood vessels. The neoplastic cells of gliomas infiltrate extensively the adjacent brain substance, but seldom if ever do they invade vascular channels. Even when the neoplasm is a glioblastoma multiforme, in which there are ruptured blood vessels and vascular thromboses, tumour cells are never seen within the blood vessels. Certainly the experimental production of gliomas in thoracic and abdominal viscera in mice by the direct injection of homogeneates from experimentally induced gliomas (Zimmerman, 1969) argues against the constant requirement by the tumour cells of a special 'soil' factor found only in the central nervous system. The ability of gliomas to grow extracranially and extraspinally under certain conditions also has been demonstrated by transplantation experiments in human volunteers. Grace and co-workers (1961) performed tumour autografts in six patients undergoing surgery because of glioblastoma multiforme; two showed successful

'takes' with proliferation of typical glioblastoma tissue in the subcutaneous tissues. Perhaps unfavourable, undetermined, immunological responses were responsible for the failures.

Astrocytoma

Astrocytic tumours fall roughly into two overlapping groups: differentiated and undifferentiated variants. The differentiated tumours, as judged by their cellular maturity, tissue texture and blood supply, have the appearance of indolent benign neoplasms. The undifferentiated members are richly cellular, more rapidly proliferating isomorphic or heteromorphic growths. There is, however, no sharp dividing line between differentiated gliomas and the undifferentiated glioblastomas. Moreover, some slow-growing astrocytomas may change into more active aggressive tumours showing evidence of cellular pleomorphism. No precise demarcation exists also between astrocytic growths and oligodendrogliomas since certain astrocytomas consist of astrocytic and oligodendrocytic elements and sometimes, in addition, spongioblast-like cells. Even some ependymal growths containing astrocytic components are not easily distinguished from astrocytomas. And that the form neoplastic astrocytes assume is not constant but variable has been shown by electron microscopy (Raimondi *et al.*, 1962).

Due to their diversity of structure the astrocytic group of gliomas has become muddled by descriptive terms which, because they do not imply the existence of distinct tumour entities, should neither be allowed to disrupt the essential uniformity of this genus of tumours nor sever its relation with other gliomas, such as the oligodendrogliomas. The astrocytic gliomas include well-differentiated variants like fibrillary, protoplasmic and 'piloid' astrocytomas, imperfectly differentiated forms such as astroblastoma or glioblastoma isomorphe and giant-cell tumours, and undifferentiated neoplasms, usually called glioblastoma or spongioblastoma multiforme. These tumefactions constitute the majority, about 75 per cent, of gliomas.

ASTROCYTOMA Well-differentiated astrocytomas are common, accounting for 25 to 30 per cent of all gliomas. They may develop at any age, but tend to occur more frequently in adults than in children. In adults it is a cerebral hemisphere, especially the temporal lobe, that is usually affected; in children it is the cerebellum, third ventricle or pons. Indeed, astrocytoma is the commonest neural tumour of childhood. Yet congenital astrocytomas are rare. Sandbank (1962) saw an astrocytoma of the left basal ganglia in a newborn infant that died 24 hours after birth. Astrocytoma of the spinal cord is an infrequent glioma of adults and is seldom seen in children. Astrocytomas of the optic nerve are also rare. They amount to about 1 per cent of intracranial tumours (*Lancet*, 1970), but tend to occur more often in children and adolescents than in adults. The prognosis is relatively good in this variant.

Some astrocytomas are either well defined or else reasonably circumscribed, differing in colour and consistency from the adjacent tissue. More often, however, and particularly in the case of the cerebral astrocytomas of adults, the growths, which may affect large portions of one or both hemispheres, are occasionally poriferous but usually non-cystic and most poorly demarcated from the surrounding brain substance. An astrocytoma may be even imperceptible in the sense that no tumefaction is discernible; only an increase in bulk of the affected region, perhaps a whole cerebral hemisphere, may be detected, the general structure of which may be largely maintained. Because of the poor cellularity of certain astrocytomas it may be impossible to demonstrate even by microscopy the exact boundary where tumour tissue terminates and normal brain substance commences. An astrocytoma with limits so imprecise is also difficult to distinguish from a generalized gliosis, and its sheer diffuseness is often more of a reflection of its widespread mode of origin (Scherer, 1938) than its capacity to infiltrate extensively.

In the rare condition called gliomatosis cerebri there is an apparent diffuse neoplastic transformation, mainly by astrocytic elements, that extends throughout the cerebral hemispheres and brain stem. Although the cellular density and morphology of such a lesion varies in some regions, and sometimes there may be marked pleomorphism with monster cells (Dunn and Kernohan, 1957), no single focus of origin is demonstrable. Nevin (1938) likened gliomatosis cerebri to von Recklinghausen's neurofibromatosis, considering that the former lesion represented a blastomatous type of malformation, a hamartomatous process related to an intrinsic anomaly of the neuroglial system. The occasional occurrence, however, of gliomatosis in von Recklinghausen's disease does not necessarily prove that an interrelationship exists, and it is more likely that gliomatosis cerebri is related to the diffuse astrocytomas.

In contrast to the cerebral astrocytoma of adults, the less common cerebellar variant, which occurs predominantly though not exclusively in children (Bucy and Gustafson, 1939; Matson, 1958; Ringertz and Nordenstam, 1951), is characteristically sharply limited but not encapsulated, the surrounding tissue exhibiting a distinct reactive gliosis. The cerebellar astrocytoma arises usually and grows symmetrically in the vermis in the midline where it forms a solid, or partly or completely cystic mass with cystic spaces, sometimes large and filled with a xanthochromic fluid. Occasionally the tumour appears as a nodule situated in the wall of a large cyst. Ordinarily a midline cerebellar astrocytoma is only moderately invasive and generally is successfully enucleated. More laterally placed lesions, however, invade more or less extensively (Ringertz and Nordenstam).

HISTOLOGICAL FEATURES

A cerebral astrocytoma is not usually a richly vascular growth and its grey, firm substance ordinarily is not discoloured by haemorrhages or areas of necrosis. The tumour stroma often shows vessels of abnormal form which may be confused in a biopsy containing little glial tissue with haemangioblastoma (Gough, 1940). Occasionally, however, there is evidence of microcystic degeneration. Characteristically the tumour consists of more or less abundant glial fibrils, in varying arrangements, and cells, some elongated and others somewhat star-shaped, in varying degrees comparable with normal astrocytes, though frequently there are piloid elements with an abundance of hair-like fibrils streaming from both ends of a rather lengthy cell body. In the same neoplasm there are cells varying from round to oval to elongated to multipolar forms and some have no processes and others have few or several processes. Even when metallic impregnation techniques are used, there may be difficulty in demonstrating that the growth is constituted predominantly or merely essentially of astrocytic elements. Different astrocytomas and different parts of the same astrocytoma may show a marked variation in the relative proportion of cells to fibrillary background (Figs. 5.1–5.4) as well as cellular diversity. All stages of transition

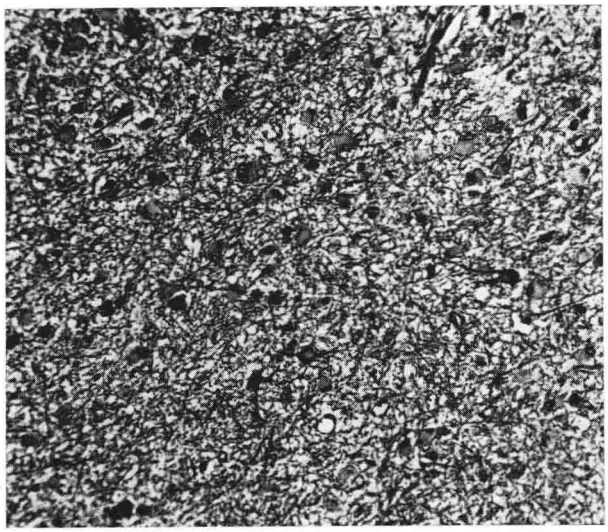

Fig. 5.1 Male aged 57 years. Diffuse, homogeneous grey white tumour of right temporal lobe. It extended medially to compress right basal ganglia and into the right parietal lobe. Some cystic change with an occasional cyst measuring as much as 1 cm across. Fibrillary astrocytoma. Astrocytes set in densely fibrillary feltwork (PTAH) ×180.

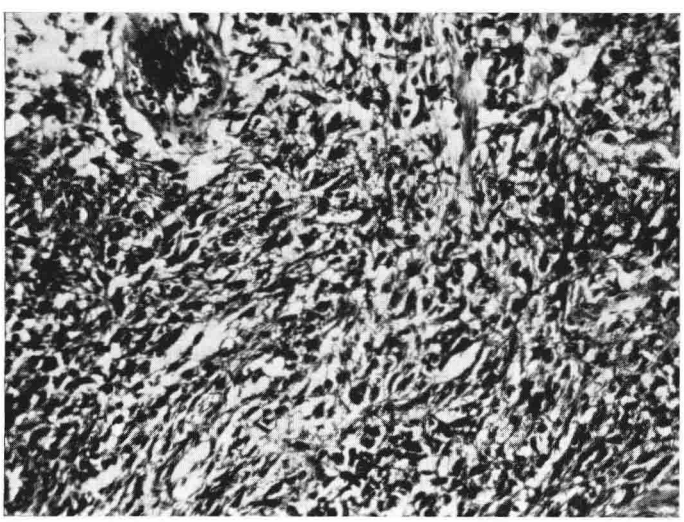

Fig. 5.2 Cellular astrocytoma of right cerebral hemisphere in male aged 58 years. (PTAH) ×165. 468/59.

from slightly to densely fibrillary astrocytomas exist and a single tumour may be fibrillary in one part and not elsewhere.

In most astrocytomas the fibrils are arranged diffusely in the fashion of an intertwining meshwork (Figs. 5.1; 5.3–5.5). Sometimes the tumour cells are small, sparse and scattered widely in an abundant neuroglial felting so dense that a scar-like aspect is imparted to the tissue. Within this network the cells appear as oval nuclei virtually independent of the glial fibrils. Often only an occasional, isolated cell with the starry features of an astrocyte is seen in such a lesion, which frequently contains small compact nuclei more characteristic of oligodendroglial cells than astrocytes, scattered throughout the quilted network. Indeed 'pure' astrocytomas are infrequent, since in a series of 200 gliomas Cooper (1935) found only 15 such tumours. In general, attendant other glial cells are not so common in the cerebellar as in the cerebral astrocytoma (Bucy and Gustafsen, 1939). Of all intracranial gliomas, perhaps cerebellar astrocytomas (Figs. 5.3 and 5.6) contain astrocytic components in the highest degree of 'purity', though these elements are frequently piloid. The development of Rosenthal fibres, the result of an excessive production of a normally occurring intracytoplasmic structure of the glial cells (Raimondi *et al.*, 1962), is common in posterior fossa astrocytomas, especially in densely pilocytic areas. Calcospherules are also frequent in these tumours.

A cerebral astrocytoma may consist largely of one kind of differentiated astrocyte: protoplasmic or fibrillary. And usually gliomas composed mostly of protoplasmic astrocytes are more cellular and poorer in fibrils (Figs. 5.2 and 5.3) than the more inert appearing fibrillary astrocytic growths. Bailey and Cushing (1926) subdivided astrocytomas into protoplasmic and fibrillary

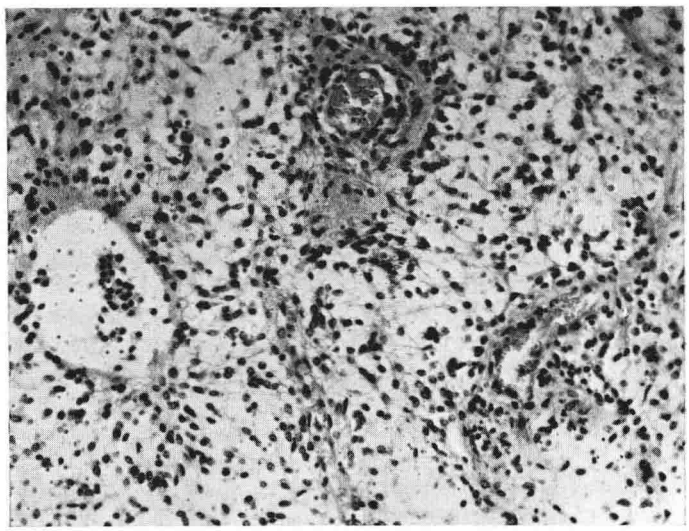

Fig. 5.3 Posterior fossa protoplasmic astrocytoma showing spongy texture, microcystic degeneration and astrocytes about the vasculature. Tumour of 2-year-old female child; partial removal of lesion followed by deep X-ray therapy. Child alive and well now, aged 12 years. (H. & E.) ×140. 26629 (*Courtesy of Dr Peter H. Buxton.*)

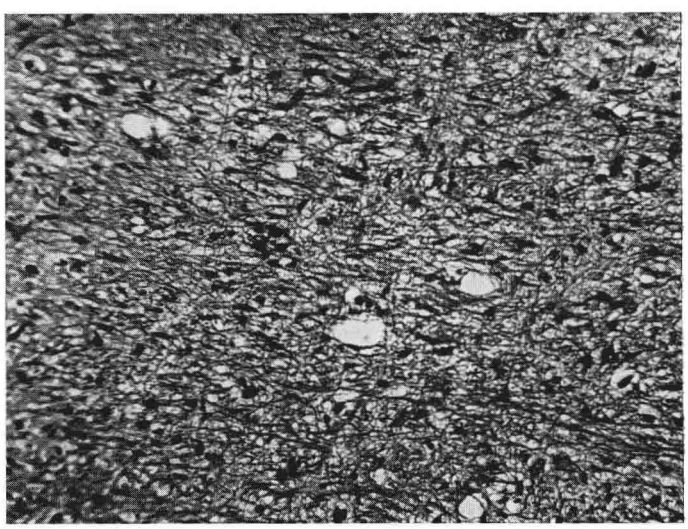

Fig. 5.4 Female aged 26 years with clinical manifestations of an intracranial tumour for only 9 months prior to death. At autopsy right cerebellar hemisphere largely replaced by tumour which crossed the mid-line into the left cerebellar peduncle and invaded widely the pons and medulla. Fibrillary astrocytoma structure in tumour invading pons. (H. & E) ×180. (12331. University of Chicago Clinics.)

types, but such a discrimination is not of much value, especially as there is no definite evidence that the predominantly fibrillary or protoplasmic variants differ significantly with respect to histogenesis and behaviour. As already stressed, astrocytic gliomas are nearly always mixtures, not only of the two varieties of astrocytes but of other cells as well, some of which may not be intrinsic neoplastic elements. Certain of the accompanying cells, especially those with small compact nuclei, are oligodendrocytes; others are obviously atypical astrocytes, but though often called spongioblasts, are of debatable histogenesis. A few non-neoplastic elements are perhaps of microglial origin.

The size, appearance and arrangement of tumour astrocytes vary greatly. Sometimes they are bigger than normal astrocytes, and now and then the round or oval, often eccentrically placed nuclei (Fig. 5.5), are conspicuously vesicular and may contain prominent nucleoli. Such cells may be confused with ganglion cells and, since the preservation of ganglion cells, and to a lesser degree of nerve fibres, is a most characteristic feature of cerebral astrocytoma, it is important to distinguish neurone-like astrocytes from true ganglion cells. Normal neurones are not part of the neoplastic process, but because they lie among the fibrillary network of the growth they sometimes effectuate the simulation of the microscopical appearances of a ganglioneuroma or ganglioglioma. Occasionally neoplastic astrocytes have blunt somewhat robust processes that are directed towards a blood vessel wall (Figs. 5.3; 5.7; 5.8). The perivascular grouping, however, is not as distinct or as prominent as in the more undifferentiated astroblastomatous growths.

Cerebral astrocytic growths are 'mixed' tumours also in the sense that well-differentiated variants may contain small or large areas of imperfectly differentiated glioblastomatous structure or that tumours predominantly composed of poorly differentiated cells show recognizable astrocytic components. According to Scherer (1940), the former should be regarded as primary astrocytomas with transformations to a more malignant tissue. Such a change may become apparent in successive biopsies or after operative intervention followed by radiotherapy.

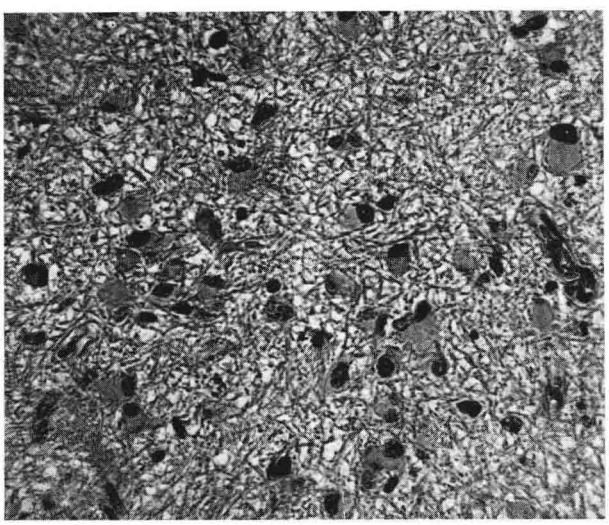

Fig. 5.5 See Fig. 5.1 for case description. Shown here are large gemistocytic type astrocytes. (PTAH) ×360.

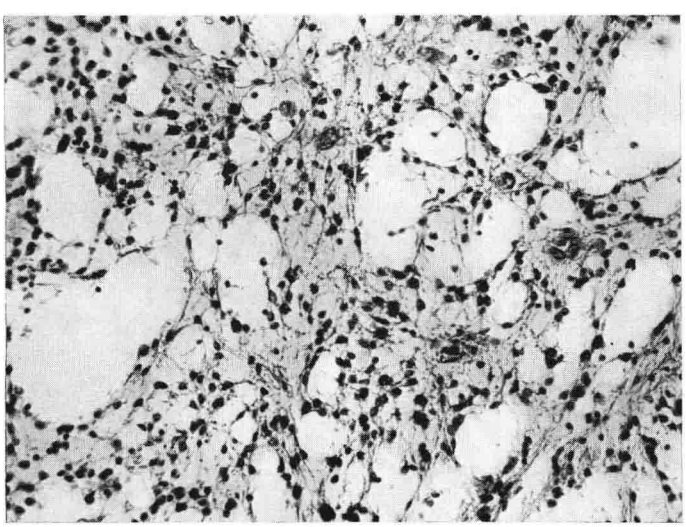

Fig. 5.6 Microcystic degeneration in extensive mid-line cerebellar astrocytoma in a child. (H. & E.) ×160. 6-204. (*Courtesy of Dr E. F. Dawson.*)

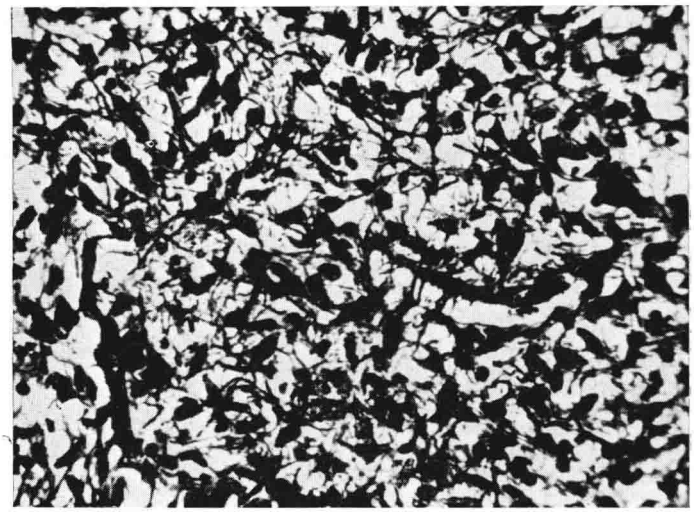

Fig. 5.7 Same tissue as Fig. 5.10 to show astrocytes some related to a blood vessel. (Silver carbonate.) ×360.

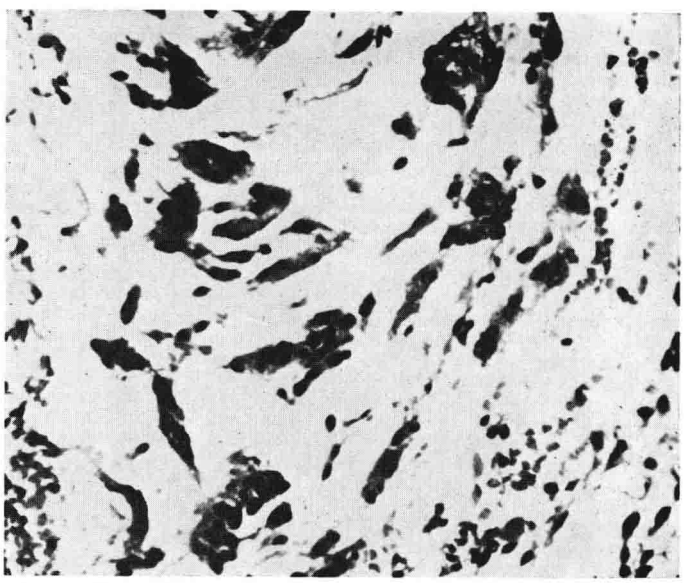

Fig. 5.8 Shows large cells with large nuclei and eosinophilic cytoplasm in a protoplasmic astrocytoma. 68/110. (H. & E.) ×400.

Figs 5.9 and 5.10

Female aged 65 years. Tumour of right cerebral peduncle involving basal ganglia. 1181/61.

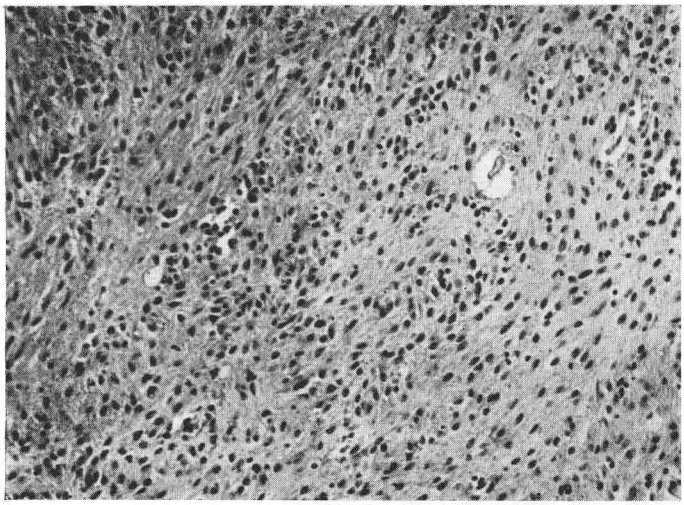

Fig. 5.9 Pilocytic astrocytoma showing fasciculated bands of piloid astrocytes. (H. & E.) ×120. 1181/61.

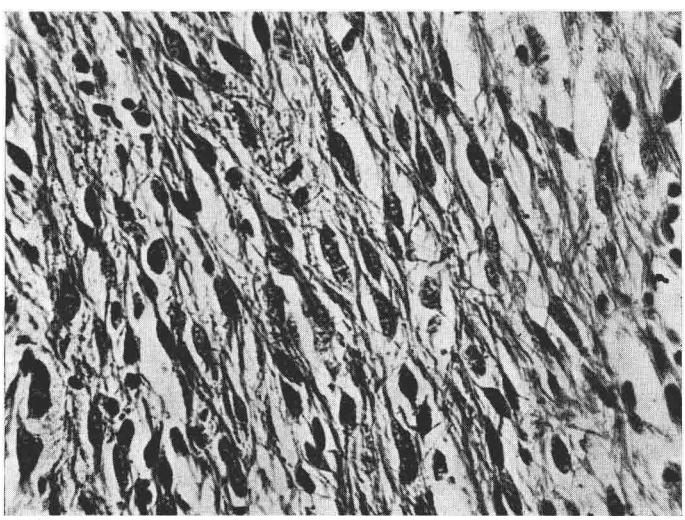

Fig. 5.10 Same as previous Figure to show pilocytic astrocytes. (PTAH) ×420.

Gemistocytic astrocytoma refers to a glioma dominated by 'gemästete' or 'stuffed' astrocytic elements, cells with abundant homogeneous opaque or hyaline eosinophilic cytoplasm and an eccentric nucleus (Fig. 5.5). Usually there is little fibril formation, but occasionally neuroglial fibrils are numerous. Although a gemistocytic astrocytoma is morphologically a distinctive tumour, yet it does not constitute a separate type of neoplasm. Neither is there any proof that this lesion represents a degenerative form of astrocytoma. Indeed, most gemistocytic astrocytomas are associated with a shorter survival than a well-differentiated piloid astrocytoma.

Penfield's (1932) piloid astrocytoma is characterized by a preponderance of more or less elongated cells lying in parallel bundles of fasciculated, long, closely packed fibrils themselves also arranged in parallel intersecting rows (Figs. 5.4; 5.9–5.12). Some cerebral, but particularly cerebellar, astrocytomas and the astrocytic growths that infiltrate the corpus callosum and pons present a largely pilocytic structure. In places stellate astrocytes are easily demonstrated, and it is likely that a pilocytic astrocytoma represents no more than an architectural variation, perhaps only an environmental adaptation, of a predominantly fibrillary astrocytoma. There is little tendency to undergo degenerative changes, but occasionally astrocytes are found orientated about a necrotic focus (Fig. 5.13) producing an effect similar to that of the 'wreath' rosette of glioblastoma multiforme. Some pilocytic cerebellar astrocytomas, because of the relatively simple morphology of their elongated tumour cells that lack a capacity to lay down an interfibrillary matrix, have been regarded as polar spongioblastomas.

The spongioblastoma polare or polar spongioblastoma (Penfield) is a rare slow-growing tumour that arises in dense tracts such as the pons, optic chiasm or cerebellum of children and young adults (Bailey, 1932; Bailey and Eisenhardt, 1932). Other sites include the third and fourth ventricles (Russell and Rubinstein, 1934). It is a debatable kind of glioma with a curious association between its occurrence in the optic chiasma

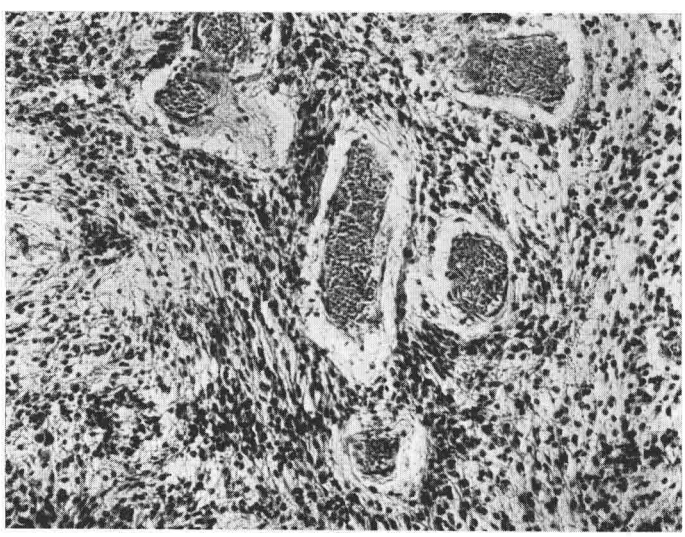

Fig. 5.11 Same as Fig. 5.6 to show spongy and compact areas and tendency of pilocytic cells to ensheath blood vessels. (H. & E.) ×120.

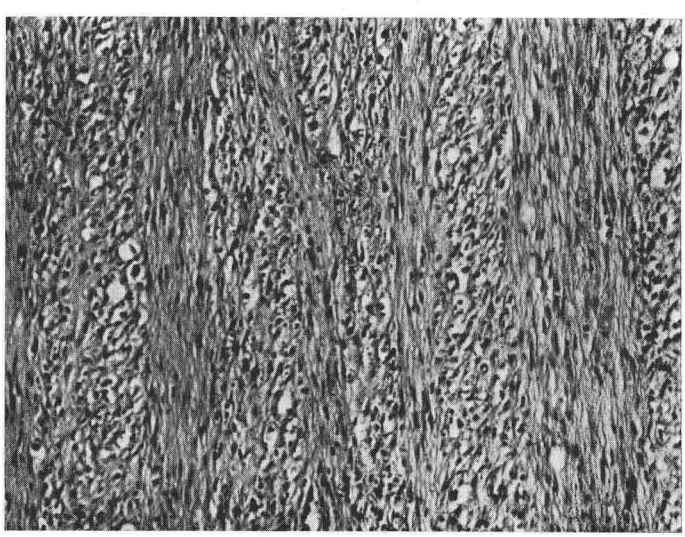

Fig. 5.12 Same tissue as Fig. 5.4 showing fasciculated structure of tumour invading pons. (H. & E.) ×120. (12331. University of Chicago Clinics.)