PATHOLOGY OF TUMOURS
OF THE
NERVOUS SYSTEM

By

DOROTHY S. RUSSELL

Sc.D., M.A., M.D., F.R.C.P.

Late Director, Bernhard Baron Institute of Pathology, London Hospital

Emeritus Professor of Morbid Anatomy, University of London

and

L. J. RUBINSTEIN

M.D.

Attending Neuropathologist, Montefiore Hospital, New York City

Associate Professor of Neuropathology, College of Physicians and Surgeons, Columbia University

Late Senior Lecturer in Morbid Anatomy, London Hospital Medical College

With a chapter on

Tissue Culture in Relation to Tumours of the Nervous System

C. E. LUMSDEN, M.D.

Professor of Pathology, University of Leeds

Hon. Consultant Pathologist, General Infirmary, Leeds

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PREFACE

It was originally planned that the late Dr. J. G. Greenfield should edit the present volume as well as its companion, *Neuropathology*, published in April, 1958. The latter purposely excluded the neoplasms of the nervous system. But in February, 1956, Dr. Greenfield intimated to the senior author that he would be unable to accomplish both tasks, and our plans had therefore to be recast.

As originally conceived, the treatment of tumours here includes those involving the peripheral as well as the central nervous system. Hence the present volume covers a wider field topographically than the recent important publications of Professor Folke Henschen (1955) in the Lubarsch-Henke *Handbuch der speziellen pathologischen Anatomie und Histologie*, and of Professor K. J. Zülch (1956) in the *Handbuch der Neurochirurgie*. But, in distinction from the latter work, we have interpreted "Tumours" on a more strictly neoplastic basis and have therefore excluded those of granulomatous and parasitic kinds. These have already been described in Dr. Greenfield's volume. On the other hand we have given considerable space to a variety of tumour-like abnormalities which, though inherently of maldevelopmental nature, are too closely allied to the true neoplasms to be disregarded.

We cannot, within their own fields, compete with the fuller texts of Henschen and Zülch, which, with their comprehensive bibliographies of the earlier literature and wealth of excellent illustrations, remain indispensable works of reference to those needing fuller information. But the march of time constantly brings new facts to light in the current journals. We have therefore sought to bring all aspects of our study fully up to date, to emphasise the more important biological aspects of the various abnormalities discussed, and to face existing difficulties of interpretation as frankly as possible. The reader may detect a strong bias in the treatment of certain controversial topics; for this no apology can be offered, since the views expressed are the outcome of convictions based upon personal study and experience. Though sincerity must dictate this course the conflicting views of other authorities are not neglected.

The departmental work provided by a large general teaching hospital has given us many opportunities of observing small and clinically silent tumours as chance findings at necropsy. These are often of peculiar value in illuminating problems of topographical origin and of histology. We have made full use of such material in our descriptions.

We hope that this volume will be of service not only to practising pathologists but to post-graduate students, neurologists and neurosurgeons. With this design many of the rarer and more difficult tumours have received lengthier treatment than is to be found in the shorter texts.

In the spirit of this work we have considered it desirable to include a chapter on the tissue-culture of the tumours of the nervous system, and we have been fortunate in obtaining the help of Professor C. E. Lumsden, whose researches in this field are widely known. His chapter reflects the essentially cytological approach of tissue-culture workers which provides a wide range of intrinsic interests and sometimes leads to provocative interpretations. The *in vitro* study of tumours is still in its infancy and it may reasonably be anticipated that, with further progress and the investigation of forms as yet untested by the method of tissue-culture, our understanding of their cytogenesis and appropriate classification will be improved, especially in the difficult glioma group.

The bibliographies appended to each chapter include those references which have seemed to us most valuable, with a certain bias in favour of those more recent publications which give useful reviews of the antecedent literature. Our warmest thanks are extended to our neurosurgical and neurological colleagues at the London Hospital for the use of their clinical records. Many other friends and colleagues have generously sent us photographs of specimens and histological material. In particular Dr. (now Professor) P. M. Daniel and Mr. Joe Pennybacker have allowed us the free use of specimens collected in the Neurosurgical Department of the Radcliffe Infirmary, Oxford. A number of our illustrations are derived from this source. Dr. W. H. McMenemey kindly provided us with Fig. 76 and histological preparations from this valuable case. We are indebted to the editors of the following journals for the reproduction of illustrations as follows: Figs. 53–55, 161 and 192 (*Brain*); Figs. 35–40, 59, 60, 130, 151 and 152 (*Journal of Pathology and Bacteriology*); Figs. 24, 29, 31, 44 and 58 (*Journal of Clinical Pathology*). Figs. 59 and 60 are taken from an article by Professor W. Blackwood, who has generously allowed their use. We also thank the C. V. Mosby Company for permission to reproduce Figs. 6, 8–10, and Butterworth and Co. (Publishers) Ltd. for the use of Figs. 26, 43, 89, 103, 163, and 202.

Our special thanks are due to Mr. H. J. Oliver for his skilled technical help; to Mr. A. John King and Mr. A. L. Gallup for unfailing care in the preparation of photographs; and to Mr. B. Conway for typographical and secretarial help. Their ready cooperation has minimised our labours.

Professor C. E. Lumsden acknowledges with pleasure the generous help afforded him by the Head Committee of the Royal Society during his tenure of the Sir Henry Head Fellowship of the Society, and his debt to the Institute of Neurology, Queen Square, and the Maida Vale Hospital for Nervous Diseases, London, for facilities and hospitality for work. It is a particular pleasure for him to be able to express here his warmest thanks to the neurosurgeons, Mr. Valentine Logue and Mr. R. H. Shephard, and also to Dr. W. H. McMenemey for the supply of tumour biopsies and clinical information. Skilled technical and photographic help were provided by Miss Risha A. Yetts, Miss Rosemary Piper, and Mr. Gordon Cox. Figures 245, 247, 252, 253, and 267 have already appeared in *Biology of Neuroglia*, 1958 (edited W. F. Windle), and grateful thanks are accorded to Mr. Charles C Thomas, Publisher, Springfield, Illinois, for permission to reproduce these.

In conclusion we are indebted to our publishers for the liberal spirit in which they have measured our requirements. The practical usefulness of a book of this kind is, in our view, largely determined by the number and range of its illustrations. Our generous treatment on this score, and the care taken in reproduction, are here recorded with gratitude.

DOROTHY S. RUSSELL
L. J. RUBINSTEIN

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PREFACE TO SECOND EDITION

The call for a new edition had given us the opportunity of bringing the text up to date. In this process we have readjusted our views when necessary, in the light of further study by ourselves and others. A section on the pituitary adenomas has been added in view of their neurological and neurosurgical importance.

Some of the illustrations have been replaced by better examples, including Fig. 20 for which we are indebted to Dr. E. J. Field.

The chapter on tissue-culture by Professor Lumsden has been considerably enlarged and contains a number of new illustrations. The need for this is partly due to the growth of his personal experience, particularly with the astrocytic gliomas and acoustic Schwannomas. In addition the publication by Kersting (1961) of a monograph, based on the tissue-culture of 357 brain tumours of all types, has allowed some gaps that were evident in the first edition to be filled, and has also enlarged our experience of the cultural characters of some of the less common types of tumour. At the same time Kersting's views have raised a number of controversial topics inevitably calling for discussion. But, apart from this major work by Kersting, the four years that have elapsed since publication of the first edition have seen little extension of studies of brain tumours by the tissue-culture technique.

The study of tumour cells by electron-microscopy is rapidly developing at the time we go to press. Whilst taking stock of the various observations so far published in this field it is, in our opinion, premature to attempt any systematic review of these findings.

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CHAPTER 1

INTRODUCTION

Incidence. Pathogenesis

A somewhat arbitrary line must be drawn between what should be included or excluded under the title "Tumours of the nervous system". Debatable points arise both topographically and in the interpretation of the word *tumour*. Apart from the essentially neoplastic proliferations of the cellular elements intrinsic to the central and peripheral nervous system should the neoplasms of the covering mesodermal sheaths be included? Embryologically the meninges are traced by some to a neuroectodermal origin, but we would hesitate to accept this argument. On the other hand the intimate relationship of the meningiomas to the neural tissues and the fact that some of these tumours even arise within the ventricles are more weighty reasons for their inclusion.

Again many texts on the intracranial tumours exclude tumours of the retina and the orbital segments of the optic nerves. We consider it logical to include the latter structures, together with the neural components of the pituitary body. Tumours of the adenohypophysis, though not of neural origin, are also discussed on account of their neurosurgical importance.

Since our concern is strictly with neoplastic disease the *granulomas* and all other manifestations of chronic inflammation are omitted, although many authors are more catholic in this respect. These conditions have more appropriately received attention in the companion volume by Greenfield *et al.* (1963), to which readers are referred. But within our conception of neoplastic disease we have found it necessary to give considerable attention to a variety of lesions that are of a maldevelopmental character, conveniently termed *hamartoma*. Some of these are virtually inseparable from the true neoplasms, both in their structure and behaviour; thus their exclusion would appear unwarrantable. In the event, however, there is slight overlapping with Norman's chapter in the book just mentioned, notably with regard to tuberose sclerosis and Sturge-Weber disease; but the angle from which these have been approached by Norman proves to be complementary rather than repetitious.

In our treatment of the peripheral nervous system we have extended the range beyond the neoplasms of the peripheral nerves to include their ganglia. This has necessitated, for obvious embryological reasons, the consideration of neuroblastomas and phaeochromocytomas together with the intermediate forms that link these with the ganglioneuromas.

General incidence of intracranial tumours

The difficulty of forming an accurate assessment of the current incidence of primary intracranial neoplasms lies in the lack of detailed and reliable statistics. Ewing (1922) recognised this and considered that brain tumours probably accounted for about 1 per cent of deaths. Peers (1936) supplied figures from the Boston City Hospital which, on analysis, agree with this. Thus of a total of 10,592 necropsies from 1896 to 1934 inclusive Peers found tumours of the central nervous system in 188. These, however, included pituitary adenomas, metastatic

and invasive tumours (secondary) and granulomas, totalling 58 cases. When these are subtracted the percentage of necropsies in which primary tumours of the central nervous system were found is 1·2. The total number of neoplasms found in other parts of the body was also assessed and 1,270 were found. Again adjusting Peers' figures for the central nervous system as above, it appears that the primary tumours of the latter formed 9·2 per cent of all those identified whether benign or malignant. This is probably as close an assessment as can be obtained, especially as Peers included a few benign intracranial tumours that were symptomless and incidental findings.

Similarly Garland and Armitage (1933) gave figures for 13,000 consecutive necropsies at Leeds General Infirmary (1910–31). They found 264 "tumours" but these included the astonishingly large number of 89 tuberculomas. Omitting these they estimated that intracranial tumours occurred in 1·34 per cent of subjects. This figure is, however, inflated by the inclusion of pituitary adenomas and metastatic neoplasms.

On a larger scale, but clearly unsatisfactory from the point of view of analysis, are the figures listed for 21 countries in the W.H.O. Report (1952) for the year 1949 and quoted by Cowdry (1955). These show that deaths attributed to "cancers of the brain and other parts of the nervous system" range from 0·2 per cent (Japan) to 2·54 per cent (Canada) of total cancer deaths. The observed variations are probably indicative of geographical differences in post-mortem procedure rather than of actual differences in the incidence of these tumours in the different countries.

Weil (1946) assembled the figures from four European centres: Vienna (1855–70), Tübingen (1892–1923), Heidelberg (1854–1931), and Freiburg (1920–37). Primary and metastatic tumours of the brain together were found in 1·81 per cent of a total of 62,142 necropsies, the primary tumours alone accounting for 1·4 per cent. Gliomas constituted 0·7 per cent, or 49 per cent of all primary brain tumours.

The latter figures agree well with our own records of primary tumours of neuroectodermal origin, given on p. 97, where we also underline the important and obvious effects that now obtain from the redistribution of cases between hospitals that are equipped with neurosurgical departments and those that are not. From this it follows that detailed accurate statistics have become impossible at the present time. For we are entirely dependent upon the larger hospitals for histological reports of sufficient accuracy for any scientific analysis: the figures issued by government departments are invalid because they give no information about the lesions included, and will obviously omit those that are incidental and not responsible for death.

Further figures, derived from large series, are given by Zülch (1956), and the comparative incidence of different types of tumour will be found in the appropriate places in later chapters of this book.

PATHOGENESIS

While any consideration of the causal factors underlying the genesis of tumours of the nervous system must naturally be related to the problem of neoplastic disease as a whole it is clear that, from its remarkably protected situation in the body, the central nervous system is normally immune from the various exogenous physical and chemical agents that are of importance in many cancers of the exposed epithelia of the body. Apart from penetrating radiations and local trauma the tissues of the brain and spinal cord can be influenced from without only by way of the circulating blood. But in spite of this relative simplification of the problem it is

unfortunately obvious that the question of pathogenesis resolves itself into the canvassing of a variety of possible factors and an empty conclusion.

On the positive side any adequate theory of neoplastic disease in the nervous system must take stock of such special features as the high incidence of tumours in childhood, the genetic determination of some, and the sex bias in the incidence of certain types of growth. Further work is needed to determine the significance and causal relationships of these factors to neoplastic disease. A considerable variety of the tumours to be described in subsequent chapters are evidently based upon maldevelopment in embryonic life, but the majority, in common with those of other tissues and organs of the body, arise in adult life and are presumably exempt from this category.

Congenital tumours

Although the existence of these is seldom established at the time of birth it is permissible to conclude, on clinical grounds, that certain others which are verified in the neonatal period have been congenital. Most of the congenital examples are primitive neuroectodermal tumours such as the retinoblastomas, medulloblastomas, neuroblastomas of the adrenal medulla, and medulloepithelioma as reported by Treip (see p. 160). In Treip's case the main growth was contiguous to a hamartoma of the leptomeninges, thus affording evidence of a maldevelopmental factor of basic importance. It is not unreasonable to argue that such cases afford some support to Cohnheim's theory of embryonic rests, now fallen into disrepute. The existence of such rests is admittedly problematical for they are seldom demonstrated in the form of undifferentiated, primitive cells. It is noteworthy, however, that Raaf and Kernohan (1944) identified nests of cells, resembling those found in medulloblastomas, in the posterior medullary velum in early life (p. 156) and postulated the origin of tumours in these. Also Cavanagh (1958) described a series of 8 cases in which small tumour-like nodules were found in the temporal lobe in association with long-standing epilepsy. These foci, of dubious neoplastic activity and possibly hamartomatous, could reasonably be interpreted as rests and, as such, the starting-point of manifest gliomas. But Cohnheim's theory has been vigorously attacked by Nicholson (1950) amongst others. He argued, fallaciously, that any embryonic rests that might occur could not survive because the cells serve no physiological function by reason of their immaturity. On the contrary, and it is implicit in Cohnheim's original thesis, it should be conceded that cells displaced during development are capable of normal maturation and persist in spite of their evident physiological inactivity. In illustration of this it is only necessary to recall the ectopic foci of grey matter occasionally found in the cerebrum (Figs. 15, 16) and the exceedingly common nests of ependymal cells found in various situations as mentioned on p. 132. These and the small ectopias of neuroglial tissue which occur in the leptomeninges and from which tumours may apparently arise (see p. 23) must reasonably be supposed to have been segregated during embryonic or early foetal life but have, nevertheless, attained cytological maturity. The weakness of Cohnheim's theory lies rather in his attribution of significant neoplastic potency to such foci. Here it must be agreed with Nicholson that ectopias share with other tissues the liability to become neoplastic but no more can be claimed. Therefore the argument now advanced is simply that the element of maldevelopment, with the segregation either of immature or mature cells, is essential to the interpretation of many forms of tumour in the central nervous system. This is of course evident and indisputable in the teratomas, dermoid and epidermoid cysts though, in the last-mentioned type, it is of interest that these may be acquired through trauma (p. 13), a mechanism that is also described and illustrated by Nicholson. The maldevelopmental aspect of these tumours is also underlined by their well-recognised association with spina bifida and cranial defects (p. 13).

The observation of cartilage and bone in ependymomas (p. 12) though exceptionally rare and puzzling seems better explained along these lines than by Nicholson's suggestion that anomalies of this character are the end-result of mucoid degeneration. Were the latter true the appearance of cartilage might be anticipated in the myxo-papillary variety of ependymoma, but this has never been observed to our knowledge.

In a different category of congenital tumours mention must be made of the choroid-plexus papillomas, since a few of these have been found at birth. No argument can be advanced for any maldevelopmental basis in these, nor is there any other recognised factor that can be held responsible for this form of neoplasia. On the other hand the colloid cysts of the third ventricle are evidently attributable to the perpetuation *in situ* of neuroectodermal structures which are normally transitional in early embryonic life (p. 142). This then is a tumour of congenital character though its presence is seldom manifest before adult life and, indeed, small clinically silent examples are occasionally discovered accidentally at post-mortem examination in middle-aged subjects.

Genetic factors

The importance of these is generally accepted in certain classes of neoplastic disease of the nervous system, though the mode of inheritance has not always been established. The retinoblastomas (see p. 185) exemplify this. In Chapter 2 we give particulars of the genetic aspects of Lindau's syndrome, tuberose sclerosis, von Recklinghausen's neurofibromatosis and some forms of neuro-cutaneous melanosis. The element of congenital maldevelopment has been widely canvassed in seeking for a rational explanation of the diverse neoplastic manifestations observed in these. The possible part played by embryonic rests, especially in tuberose sclerosis and von Recklinghausen's disease, cannot be entirely ignored when the widely scattered microscopic foci of abnormal cells in the central nervous system that are to be found in these two diseases are recalled (pp. 30, 36). Though morphologically these cells cannot justly be called embryonic it is of interest that Nicholson accepted, though with manifest reluctance, those demonstrated in tuberose sclerosis as embryonic rests in the sense postulated by Cohnheim. A relationship between these cell nests and neoplasms is by no means obvious, though we have advanced some evidence (p. 106) that such exists (see also Norman's account, 1963) and the occasional published reports of diffuse cerebral gliomas in both tuberose sclerosis and von Recklinghausen's disease might theoretically be explained in terms of multifocal neoplasia with secondary confluence of the foci. But such a process has so far not been demonstrated. The suspicion is, however, strengthened by the observation of malignant transformation in those rare cases of megalencephaly in which this condition is associated with a diffuse overgrowth of protoplasmic astrocytes (Norman, 1963, p. 352).

In tuberose sclerosis the argument for embryonic cell nests can be extended to the neoplasms observed in other organs, notably the kidneys and heart, but it appears to break down in von Recklinghausen's disease in respect of the tumours arising in the meninges, nerve-roots and peripheral nerves: the argument that these, especially the plexiform neurofibromas, are based upon maldevelopment commends itself as likely, but is still hypothetical.

The familial occurrence of other tumours, especially gliomas, has occasionally been noted and it is true that medulloblastomas have occasionally been encountered in identical twins (for references see Zülch). Koch (1954) examined the literature from this angle and concluded that there was some support for a genetic factor in certain cases of glioblastoma. This was not confirmed by Harvald and Hauge (1956) in their exhaustive investigation of a large and well-controlled series. Their more recent analysis (1960) of intracranial tumours, including also astrocytoma, meningioma, acoustic neurinoma and medulloblastoma, yielded

similar results with the possible exception of astrocytoma, in which the familial incidence was slightly greater than anticipated. Kjellin *et al.* (1960) again cast suspicion upon the astrocytomas, which cropped up in 5 of the 7 families studied by them.

Factors in post-natal life

Trauma. This has been invoked as a provocative factor in a variety of human neoplasms. It is undoubtedly true that a blow on the head, possibly insufficient to cause more than local bruising of the scalp, can unmask a glioma already present. The mechanism here appears to be the setting up of oedema in tissues adjacent to the growth, as discussed in Chapter 11. In the event the time interval is too short to attribute the tumour to trauma.

The problem is more difficult when a period of months or even years has elapsed. The medico-legal aspects of this were carefully examined by Ewing (1935). His paper should be consulted for the earlier literature and debate as to the significance of trauma in the aetiology of intracranial tumours. He concluded that the unequivocal demonstration of a glioma at the actual site of an old injury, and after an interval of time sufficiently long to permit of tissue-regeneration, went some way to establish cause and effect. But cases have rarely been recorded that satisfy these requirements. Apart from those mentioned by Ewing, and recapitulated recently by Heyck (1954), we may note the latter author's personal observation of a bifrontal glioblastoma, of butterfly form in coronal section, at the site of leucotomy performed 5 years earlier. The patient, a woman aged 51, had suffered from schizophrenia for the preceding 36 years: a length of time that precludes the attribution of her mental state to the glioma. In addition Finkemeyer and Behrend (1956) identified a protoplasmic astrocytoma, in a man aged 35, at the precise site of a shell-injury of the brain sustained 9 years earlier. Microscopically the tumour was in direct continuity with the scar tissue of the dura and superficial tissues.

Our own series includes the case of a man aged 22, from whom a superficially situated anaplastic pilocytic astrocytoma (see Figs. 128, 129, p. 148) of the right parietal lobe was successfully removed $6\frac{1}{2}$ years ago and who is at present well and free from symptoms. He received a minor head-injury at the age of 13 whilst playing football. Later that day he had headache and stated that he lost consciousness but was well the following morning. A year later he began having fits of a purely sensory character in the left hand. Occasionally these were accompanied by loss of consciousness. There was no family history of epilepsy. On account of the increase in frequency of the fits he was investigated 8 years later when he was found to have thinning and bulging of the vault of the skull in the right parietal region, but no other objective physical signs. Exploration of the area through a burr-hole disclosed a subdural collection of clear yellow fluid and 2 ml. were withdrawn. Biopsy of a few fragments of the leptomeninges revealed no tumour. Since this measure did not relieve his attacks, craniotomy was performed 16 months later and this exposed a relatively circumscribed glioma which infiltrated the dura mater (Fig. 128). The tumour was completely removed and no subsequent X-irradiation was considered necessary. The defect in this story lies in the lack of any precise evidence concerning the site of initial trauma, and the failure to identify any scar tissue in relation to the tumour. The sequence of events is, however, suggestive and sufficiently remarkable to warrant this record.

On the other hand when the vast legacy of war and civil brain-injuries, uncomplicated by neoplastic disease, is weighed in the balance it must be concluded that these few cases are more curious than significant.

Trauma has also been invoked in the pathogenesis of *meningiomas*. Cushing and Eisenhardt (1938) considered that the incidence of these tumours over the cerebral convexities at

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the precise site of an antecedent lesion, demonstrated by a scar, was significantly high. This view was also supported by Penfield (1932), who quoted a case in which fragments of coal were identified in the scalp overlying a meningioma: the residue of an injury incurred 2 years before operation. He also held that trauma played a part in the production of the cranial hyperostosis sometimes found in conjunction with meningiomas. Yet this bony thickening, though commoner over the vertex, can also occur at the base particularly in the region of the sphenoidal ridge. Its dependence upon antecedent trauma is therefore highly questionable.

The reader is referred to the section on meningiomas (p. 44) where further particulars are given, including the exceptional case of Reinhardt (1928) in which trauma could reasonably be invoked in the genesis of a meningeal sarcoma.

Iatrogenic trauma may involve the dislocation of normal or neoplastic cells into sites where their further proliferation is permissible, as in lumbar epidermoid cysts (see p. 13).

Infections and inflammations. Little can be entered in support of these as factors in tumour-formation. The search for intracellular parasites (Jackson, 1948; Krynauw and Jackson, 1948) is still pursued and it is of interest that Jackson considered that all gradations between foci of chronic encephalitis and glioma (astrocytoma) could be demonstrated in the domestic fowl. We note elsewhere (p. 153) the personal observation of a case in which two topographically distinct gliomas were related to the plaques of multiple sclerosis, but the incidence of this association has so rarely been observed that its significance, if any, is obscure.

The virus theory of carcinogenesis, still actively supported on experimental grounds, must be held in reserve in relation to human tumours. The reported occurrence of intranuclear "inclusion bodies" (Russell, 1932; Wolf and Orton, 1933), especially in the glioblastomas, must in retrospect be regarded as of doubtful importance in this connection. They were also noted in meningiomas and "perineurial fibroblastomas" by Wolf and Orton. Their appearance in cultures of meningiomas was further investigated by Bland and Russell (1938) but similar inclusions were later identified in cultures of human foetal leptomeninges (Fischmann and Russell, 1940), and in the last report the difficulties of accepting a virus origin of the inclusions were discussed.

Chemical carcinogens

The production of intracranial tumours, mainly gliomas, has been repeatedly achieved by experimental means in rodents. The four obtained by *oral* administration of 2-acetylaminofluorene (Vazquez-Lopez, 1945, 1 tumour; Hoch-Ligeti and Russell, 1950, 3 tumours) are the only examples known to us in which this route has been successfully employed. Three of the tumours were cerebral glioblastomas, one of which had certain cytological features suggestive of oligodendroglioma; the fourth (Hoch-Ligeti and Russell) was an encapsulated meningioma of considerable size, apparently arising from the cerebral leptomeninges and unattached to the dura. Since spontaneous intracranial tumours are extraordinarily rare in rodents these results were held to be significant. The carcinogen employed gives rise more frequently to tumours in other organs in the rat, especially the liver. Hoch-Ligeti (1948) also observed overgrowth of the interstitial cells of the gonads in treated rats, and found that the oestrous cycle was suppressed. The intracranial tumours in her experiments were not manifest until the animals had been treated for 10 to 14 months. Hence it is conceivable that these results were attributable to secondary hormonal disturbance rather than to the carcinogen primarily; this appears the more likely when the relative impermeability of the cerebral capillaries is recalled.

The possibility that hormonal imbalance may play some part in the evolution of the commoner gliomas of late adult life merits further investigation. Analysis of large series of both astrocytomas and glioblastomas shows a strong preponderance in the male sex (Henschen, 1955).

On the other hand meningiomas are commoner in women than in men and it is of interest that pregnancy may evoke oculomotor and other pressure-symptoms from a meningioma that is clinically silent both before and after pregnancy (Bickerstaff *et al.*, 1958). These authors argue that expansion of the tumour in pregnancy is due to oedema resulting from a disturbance in the water-balance. There is histological support for this argument, but the problem merits further investigation.

The experimental production of pituitary adenomas in rats and mice by hormonal disturbance is extensively documented (Giok, 1961). The means commonly used are the administration of oestrone, or one of the thyroid-blocking techniques. There are, however, salient differences between rats and mice, and between different strains of mice, in the results observed so that the wider implications of these observations remain uncertain.

Local implantation of carcinogens. Though this highly artificial means of inducing neoplasms has no direct bearing upon the spontaneous tumours of man the results of such experiments are of intrinsic interest in relation to the cytology of the gliomas and their classification.

The usual method employed has been the direct introduction of the carcinogen as a pellet into the brain. Thus Seligman *et al.* (1939) produced a considerable variety of gliomas in mice by the use of methylcholanthrene. This has been abundantly confirmed (Peers, 1940 Zimmerman and Arnold, 1941; 1943) and Zimmerman has more recently (1955) recapitulated the results of a series of experiments in which he and different associated workers observed the cytological effects of transplanting portions of the induced cerebral tumours into the subcutaneous tissues of homologous animals and thence into the allantoic membrane of the chick egg. Surprisingly, as related, an ependymoma established in the subcutaneous tissues became completely unrecognisable as more than an amorphous mass of malignant tumour cells in the egg but, when transferred back to the mouse, reassumed the characteristic morphology of the original tumour. From this it is argued that the environment or host provides factors that determine the cytological appearance of the tumour cells.

From these experiments it is clear, as Zimmerman points out, that the cytological character of the tumour evoked by the carcinogen depends in large measure upon the site at which the latter is implanted: an ependymoma results when the pellet impinges on the ventricular wall, and so forth. But these experimental gliomas tend also to develop as a mixture of glial forms, derived from various elements of the host's tissues at the site of implantation. This is by no means surprising when the neoplastic potentialities of all forms of glia in the human subject are recalled. Moreover, as will be seen in our later discussion of the glioma group, many of these human tumours display mixed cell-populations: in some the mixture is of an intimate character, in others the variation is of a more geographical kind where a sharp transition in the microscopical appearances is obvious on moving from one field to another. This variability is not to be confused with the polymorphism associated with anaplasia; the latter proposes a totally different problem in cytological analysis.

In the induction of experimental gliomas by the implantation technique it is clear, from the publications quoted, that the factor of constitutional susceptibility in different strains of mice is as important here as in other kinds of experimental neoplasms in these animals. The implications of this, however, have no obvious bearing upon human tumours in the present state of our knowledge. By using a similar technique Causey (1960) produced malignant tumours of the sciatic nerve in mice. The incidence of tumours was appreciably increased by crushing the nerve proximal to the site of injection of the carcinogen; an observation strongly supporting his contention that a neoplastic proliferation of Schwann cells accounted for the intraneural growths, in distinction from those that arose outside the intact perineurium which he interpreted as fibrosarcomas. The latter were more apt to arise when the nerve had not been crushed.

The possibilities of **transplanting** tumours to heterologous species have been investigated at Yale University (Greene, 1951), the anterior chamber of the guinea-pig eye being successfully

used as an initial site for the implantation of a human glioblastoma with subsequent transfer of the tumour to the brains of experimental animals. In guinea-pigs the cerebral growths recapitulated histologically the features of the parent tumour, but in mice the transplants became more undifferentiated and sarcomatous in appearance. In further experiments Greene successfully transferred three human glioblastomas directly to the brains of guinea-pigs and mice, with similar histological results, but ependymomas and astrocytomas failed both by this technique and when transferred to the guinea-pig's eye. The highly malignant character of glioblastomas probably accounted for the success in experiments with this type.

Irradiation

Penetrating X-rays, therapeutically used in the treatment of intracranial and intraspinal tumours, may conquer the neoplasm towards which they are directed and yet induce a series of changes in the non-neoplastic nervous tissue that cumulatively simulate a recurrence of the growth clinically. Even on macroscopic examination of the brain these localised irradiation changes bear a superficial resemblance to a diffuse glioma; especially glioblastoma multiforme, but the histological appearances are distinctive (Pennybacker and Russell, 1948). Although the neuroglial elements in these areas present abnormally large and bizarre forms there is no evidence so far that these alterations go on to neoplastic activity. But the fact that, in experimental conditions, the abnormal changes display a tendency to spread into regions beyond the immediate confines of the irradiated area (Russell *et al.*, 1949) is suggestive, and it is desirable to leave this question *sub judice*, as far as the glia is concerned.

The possibility that therapeutic irradiation may incite malignant *mesodermal* neoplasms is suggested by occasional published reports as mentioned on p. 60. This sequence is paralleled in a personal observation. In this case a circumscribed giant-celled glioblastoma was successfully, and apparently totally, removed from the frontal lobe of a male aged 18 years. The operation was followed by a course of deep X-ray therapy. Six years later he presented with a massive, and ultimately fatal, tumour which had arisen in the dura at the site of operation. This proved histologically to be a fibrosarcoma. The long interval of freedom between these events, and the essential dissimilarity in the histological appearances of the tumours inevitably create the suspicion that the irradiation at least played some part. It is of interest that the latent period in these cases has been of rather similar duration.

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CHAPTER 2

CONGENITAL TUMOURS OF MALDEVELOPMENTAL ORIGIN

Without prejudice to the various theories concerning the pathogenesis of neoplastic disease, there are certain tumours which, from their histological structure, are clearly alien to the tissues in which they lie and are thus reasonably interpreted as the outcome of perverted development in embryogenesis. Moreover they are not infrequently associated with congenital malformations elsewhere of a non-neoplastic nature, for example spina bifida. The central nervous system, and especially the brain, is notably affected by a variety of tumours of this character.

It is proposed therefore to give a general account of the teratomas, dermoid and epidermoid cysts and cholesteatomas. The closely allied craniopharyngioma (or suprasellar cyst) is conveniently treated in this context.

A second category is formed by a variety of tumours, distinct from the above but kindred inasmuch as they are evidently based upon ectopias of developmental origin. Certain of these, of neural structure, are peripherally situated. Collectively such tumours are conveniently classed as *hamartomas* (Albrecht, 1904), but their claim to be regarded as neoplasms is based upon their biological behaviour as tumours together with their macroscopic appearance rather than upon their microscopic character since some display little or no evidence of growth by cellular proliferation. The latter may then be indistinguishable from certain ectopias, best exemplified by the small but well-defined group of cases in which a mass of neural tissue, attached to the ventral surface of the hypothalamus, is usually associated with precocious puberty (p. 25).

Finally consideration must be given to those groups of diseases in which a genetic and familial element determines the individual expression of multiple lesions, some of which may, biologically speaking, be clearly neoplastic both in their behaviour and histological appearances, while others are more easily explicable as pure maldevelopments, for example in Lindau's syndrome and tuberose sclerosis.

1. *TERATOMAS AND TERATOID TUMOURS*

As defined by Willis (1960) "a teratoma is a true tumour or neoplasm composed of multiple tissues of kinds foreign to the part in which it arises". This simple statement obviously covers those forms which others have called "teratoid": a term for which Willis has no use. In the progress of growth some teratomas acquire malignant features and these, according to Willis, almost always display some tissue elements which are embryologically immature.

Although many include dermoid cysts in this group, and indeed their separation is academic, it will be convenient here to class them apart on account of their distinctive features.

Incidence. As intracranial growths teratomas are rare, constituting about 0·5 per cent of the total (Zülch, 1956). But this incidence increases to 2·0 per cent if children below the age of 15 years are selected (Ingraham and Bailey, 1946). In the spinal canal, excluding the relatively common sacrococcygeal form, teratomas seem even rarer for they do not figure in Kernohan and Sayre's (1952) analysis of 979 tumours. Hosoi (1931), however, reviewed 9 verified examples in the literature in addition to an original case, and Furtado and Marques (1951) have listed 3 further acceptable cases in adults. Ingraham and Bailey also identified 6 examples in their series of juvenile cases, and Henschen (1955) gives individual notes of some others but it is not clear whether certain of these should not rather be interpreted as hamartomas. Müller and Wohlfart (1947) also found that spinal teratomas were very rare.

Sex and age. Intracranial examples are commoner in males owing to the great tendency for the pineal body to be involved (see below). In the neonatal period, however, Greenhouse and Neubuerger (1960) found most in females in their series of 25 cases, and the same tendency has been noted in teratomas of the spinal canal (Willis). Growths in either site are mostly observed in the first decade, but occasionally they become manifest in middle life.

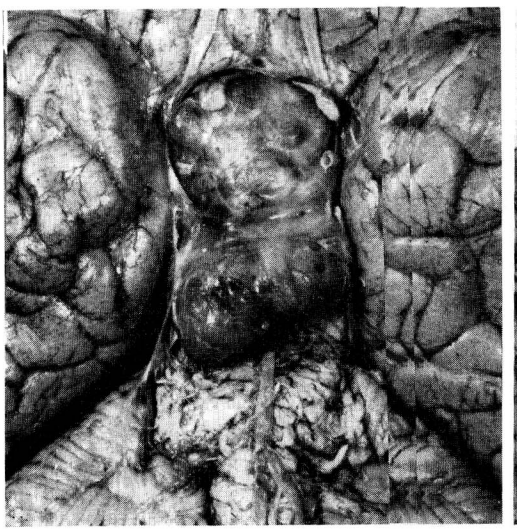

FIG. 1

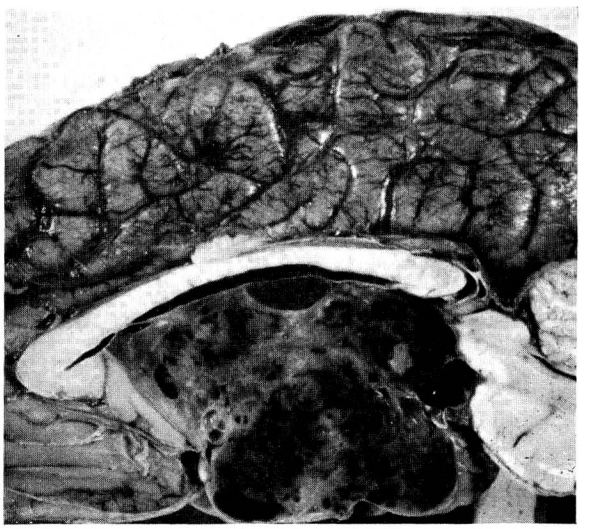

FIG. 2

FIG. 1. Suprasellar teratoma in boy aged 8; basal view.
FIG. 2. As in Fig 1; mid-sagittal.

Sites. 1. *Intracranial.* The pineal body is chiefly affected. Thus in an analysis of 94 reported cases involving the brain Sweet (1940) found 39 at this site. The pituitary came next in frequency (15 cases) and then the posterior fossa (10 cases). The remainder were widely distributed, a few being so massive that the greater part of the brain was replaced. Müller and Wohlfart accepted 84 reported cases of intracranial teratomas and teratoid tumours, and of these 46 were pineal; the remainder favoured mid-line situations, especially the pituitary and third ventricle (see Figs. 1, 2).

2. *Spinal cord.* Dorsal or dorso-lateral situations are usual and the growth may be extra- or intradural, or intramedullary. Various levels are affected: in Ingraham and Bailey's 6 cases 3 were lumbar, 2 cervical and 1 thoracic. Spina bifida, usually occulta, is often associated (see Cameron, 1957, for references).

Pathological appearances. These are summarised in the chapter on pineal tumours

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