Pathology of Tumours of the Nervous System

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4TH EDITION

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Preface to the Fourth Edition

Twenty years have elapsed since we undertook the first edition of this book. The approval that it received throughout its successive editions has encouraged us to maintain its general format while paying due heed to the various developments in neurooncology that have taken place in the past two decades.

The last seven years have been especially fruitful in this regard. Considerable advances have been made in particular in the techniques and applications of experimental neurooncology, whose contributions have greatly added to our understanding of the cellular biology of neural neoplasia. The body of knowledge that is now rapidly accumulating in this field is undoubtedly presenting us with the increasingly difficult problem of assimilating, let alone critically evaluating, a profusion of data which span an ever-widening range across both the clinical and basic sciences. As far as possible we have selected those aspects in recent trends that seemed to us immediately relevant to our purpose, realising that in a fast-moving field some of the information that appears pertinent to us at this time may have to be modified or eliminated in the years to come. The sections which in this context have needed most extensive revision are those concerned with the experimental production of tumours of the nervous system with alkylating agents and oncogenic viruses; with the involvement of the central nervous system in leukaemia and lymphoma; and with the endocrinological aspects of the pituitary adenomas. Our experience of such rare entities as the medulloepithelioma, the cerebral neuroblastoma and the tumours of the pineal parenchyma has appreciably increased, and will be reflected by a more complete account of these neoplasms. The current controversy on the nosological status of the angioblastic meningioma and its relationship to the haemangiopericytoma seemed to us to merit detailed reappraisal at this time. We have taken due notice of the further contributions made by electron microscopy to our better understanding of the cellular composition of such tumours as the capillary haemangioblastoma, the ependymoma, the medulloblastoma, the ganglioglioma, and the retinoblastoma. More than fifty new illustrations, of which approximately half are electron micrographs, have been addded to the text.

In preparing this fourth edition we record with the deepest regret the death of our former collaborator, Professor C. E. Lumsden, in June 1974. In consequence, the book has needed some reshaping, and modified excerpts of his chapter on the tissue culture of tumours have, together with selected photomicrographs, been incorporated in appropriate relationship to other parts of our text. This has enabled us to take stock of other recent advances in the field of tissue culture. We hope that the more compact character of this edition will recommend itself to the reader. Those who wish to study the more theoretical, practical and historical aspects of tissue culture should refer to Lumsden's separate chapter in our third edition (1971).

In this edition, as in previous ones, particular attention has been paid to a number of unusual tumour entities, many of which have been referred to us for consultation in recent

years. We express our warm gratitude to the numerous colleagues and friends who have thus enlarged our experience by providing us with invaluable new and rare pathological material. We also wish to record our thanks to the several co-workers, in particular those past and present members of the Stanford graduate neuropathology programme, who have collaborated in the various clinical and experimental aspects of the new work incorporated in this edition. We are especially indebted to Dr Mary M. Herman for the close collaboration, expert advice and unstinted support she has given for many years, from both the practical and the conceptual standpoint, to our joint studies in the areas of tissue and organ culture, and of electron microscopy.

We express our thanks to Dr Arthur Arnold for the scanning electron micrographs reproduced in Figs. 50, 89, 113 and 171; to Dr Juan E. Olvera Rabiela for the photograph of Fig. 195; and to Professor C. E. Hedinger for the photograph of Fig. 212. We are indebted to the editors of the following journals for permission to reproduce illustrations as follows: Figs. 150, 151, 157, 158, 285, 286 (*Acta Neuropathologica*); Figs. 159–161 (*Archives of Pathology*); Figs. 87, 88, 172 (*American Journal of Pathology*); Figs. 69, 70, 192 (*Cancer*); Figs. 85, 203–205 (*Journal of Neurological Sciences*); Figs. 310–312 (*Journal of Neurosurgery*); Figs. 209–211 (*Journal of Pathology*); Figs. 115, 148 (*Neuropathology and Applied Neurobiology*). We also thank the North-Holland Publishing Company, Amsterdam, for permission to reproduce Fig. 188.

Our special thanks are due to Mrs Melinda Callahan and Mrs Barbara Law for typographical and secretarial help in the preparation of the text.

Finally, we are indebted to our publishers for the liberal spirit in which they have met our requirements. In particular we record our appreciation to Miss Barbara Koster and Mr W. R. Smeeton for the numerous courtesies extended to us in the publication of this fourth edition.

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LUCIEN J. RUBINSTEIN

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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, *Greenfield's Neuropathology* (1976), 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 the chapter on malformations of the nervous system in the book just mentioned, notably with regard to tuberose sclerosis and Sturge-Weber disease; but the angle from which these have been approached in the companion volume 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 1270 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. 150, 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 very difficult to obtain 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. A consistent statistical approach to the problem is, however, exemplified by the analysis of Percy *et al.* (1972) on the incidence and survival of patients with various central nervous system tumours in a single indigenous population viewed over a period of 34 years. Such a survey, on an admittedly limited but carefully studied population, indicated that only 58 per cent of the cerebral and spinal tumours recorded were primary and that, among these, meningiomas were slightly more frequent than gliomas, a finding that apparently reflects the relative prevalence of meningiomas in the primary central nervous system neoplasms that are uncovered first at autopsy.

Further figures, derived from large series, are given by Zülch (1956). The epidemiological approach to the incidence and prevalence of brain tumours, with emphasis on the planned statistical analysis of relatively small, highly selected populations, has been reviewed by Behrend (1974). Such studies indicate relatively wide variations in the incidence rate of primary cerebral tumours per 100 000 inhabitants, ranging from approximately 7 to 13, but whether these variations, which are largely geographical, are significant is obscure. From

Behrend's analysis, few definite conclusions emerge: the incidence rate of primary cerebral tumours is probably the same for most races, with the exception of black individuals, in whom it is appreciably lower than in white; the incidence of intracranial tumours in general appears to increase steadily with age; and intracranial germinomas are notably more frequent in Japan than elsewhere. 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. The possible significance of the first two of these features in regard to neoplastic causation is briefly discussed below. Further work is obviously needed to probe more deeply into the relationship of these factors to neoplastic disease. In any event, while a considerable variety of the tumours to be described in subsequent chapters are evidently based upon maldevelopment in embryonal life, 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 and tumours of presumed embryonal origin

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. Such cases include a wide variety of neuroectodermal, mesenchymal and maldevelopmental tumours, which have been adequately reviewed by Solitare and Krigman (1964) and, more recently, by Jellinger and Sunder-Plassmann (1973). Of particular importance in these congenital examples are primitive neuroectodermal tumours such as the retinoblastomas, medulloblastomas, neuroblastomas of the adrenal medulla, and medulloepithelioma as reported by Treip (see p. 256). 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 fully developed brain, 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. 246) and postulated the origin of tumours in these. The oncogenic potential of such cells is, on the other hand, difficult to determine, since more recent studies have shown that similar cell nests can be found in the cerebellar nuclei of infant autopsy

material in a high percentage of cases, amounting to almost 40 per cent in one series (Jellinger, 1972; Friede, 1973): these nests apparently undergo dissolution by the fourth month of birth, at the same time as the fetal granular layer. The latter may also, occasionally, show focal persistence, even in the adult (Brzustowicz and Kernohan, 1952), and we have noted elsewhere a similar phenomenon in the cerebellar cortex of an 11-year-old female with hydrocephalus (Rubinstein, 1975). Evidence based on personal observation will also be presented on p. 245 in support of the view, originally proposed by Stevenson and Echlin (1934), that medulloblastomas may be derived, in some cases, from a neoplastic proliferation of the external granular layer or its remnants (Kadin *et al.*, 1970).

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. 204. These and the small ectopias of neuroglial tissue which occur in the leptomeninges and from which tumours may apparently arise (see p. 40) must reasonably be supposed to have been segregated during embryonic or early fetal 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. The cerebral medulloepithelioma with divergent ependymal and neuronal differentiation reported by Deck (1969) illustrates the point: in this case, the tumour was unrelated to the ventricular system and must therefore have arisen from embryonal cells that had migrated from the primitive mantle layer, yet had retained their multipotentiality.

The element of maldevelopment is of course evident and indisputable in the teratomas, which account for a relatively high proportion of described congenital intracranial tumours (Solitare and Krigman), probably because of selective reporting; and of dermoid and epidermoid cysts although, in the last-mentioned type, it is of interest that these may be acquired through trauma (p. 29), 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. 29).

Germane to these considerations are three aspects of neoplastic development that seem to play a special role in certain forms of neuroectodermal tumour. First, the relatively high frequency of central and peripheral nervous system tumours in early life suggests that fetal neuroepithelial cells might be a selected target for subsequent neoplastic development, a view which apparently gains support from a large statistical study of children with cerebral and spinal cord tumours that correlated age at diagnosis and risk of late recurrence (Stewart *et al.*, 1973). The second aspect, discussed in greater detail elsewhere (Rubinstein, 1972), is the prevalence in childhood of primitive central neuroepithelial tumours with potential differentiation along lines that follow the stages of normal neurocytogenesis. Examples include not only the medulloepithelioma but also the cerebral neuroblastoma, the polar spongioblastoma,

the ependymoblastoma, and the cerebellar medulloblastoma. Thirdly, these tumours exemplify a concept of neoplastic development that emphasises as its basic mechanism altered patterns of gene expression rather than the prevailing contemporary view that neoplastic mechanisms are primarily genetic. Taken from that angle, neoplasia is considered to be a disease of cell differentiation. This concept is illustrated by the experiments of Artzt and Bennett (1972), which are relevant in the present context. Using mice carrying a specific allele that causes defective primitive-streak formation and its subsequent overgrowth in homozygous animals, they implanted these genetically aberrant embryos into the testes of normal adult mice, which then developed tumours that included extensive areas of embryonal neuroepithelial tissue corresponding to medulloepithelioma, medulloblastoma and neuroblastoma. In this instance, therefore, a genetically determined block in the normal sequence of development expressed itself in an embryonal tumour of predominantly neural origin.

As argued on p. 28, the observation of cartilage and bone in mid-line posterior fossa ependymomas and astrocytomas, an exceptionally rare and puzzling phenomenon, is possibly explained on the basis of an unusual inductive interaction of a maldevelopmental nature between neoplastic neuroepithelial cells and included mesenchymal elements rather than by Nicholson's suggestion that it is the end-result of mucoid degeneration. Were the latter true, the appearance of cartilage might be anticipated in the myxopapillary 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 number of these have been found at birth. Except in the case of a rare form of bilateral villous hypertrophy of the choroid plexus (p. 220), no argument can be advanced for any maldevelopmental basis in these tumours, 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, in most cases, apparently attributable to the abnormal folding in situ of structures derived from the primitive neuroepithelium, although an alternative origin from included endodermal cell nests has recently been suggested (p. 226). In any event, this 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. Progress has, however, been made in recent years in elucidating the mode of inheritance of retinoblastomas (see p. 301). On the incidence of this tumour has been framed a hypothesis of neoplastic development that postulates a double mutational event implicating both germinal and somatic cells in some cases, and somatic cells only in others (Knudson, 1971). 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. 47, 54). 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. 48) that such exists (see also *Greenfield's Neuropathology*, 1976, p. 413), 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 (*op. cit.*, 1976, p. 390).

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. Of interest in this regard, however, is a study on these tumours using genetic enzyme cell-markers (Fialkow *et al.*, 1971): this has established that the neurofibromas in this disease must each have a multiple cell origin, with the corollary that either the initial oncogenic event must simultaneously implicate a large number of cells or, alternatively, a neoplastic change in one or a few cells may subsequently induce a similar change in its neighbours. The findings of course reinforce the well-accepted view that in this disorder neoplastic changes are genetically determined.

Elsewhere (p. 247) we also note the association, established in a few cases, of cerebellar medulloblastoma with the recently described syndrome of multiple basal-cell naevi.

The familial occurrence of nervous system tumours, especially gliomas, outside the framework of the dysgenetic syndromes referred to above, has sometimes been recorded, and it is true that medulloblastomas have occasionally been encountered in identical twins (for references, see Zülch and Mennel, 1974). 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. The available literature on familial glioblastomas has since been reviewed by Manuelidis (1972a), who concluded that inherited factors had not been shown to play any major role in their incidence.

Chromosomal aberrations

The finding of chromosomal abnormalities in poorly differentiated gliomas (for references and review, see Zülch and Mennel) is of course not unexpected in view of the anaplastic nature of these tumours and does not therefore help to unravel the causal relationship between genetic constitution and malignant growth. Of more significance in this context, however, are observations on the chromosomal constitution of well-differentiated meningiomas, in which, according to the work of Zang and his co-workers, one G chromosome, identified as number 22, appears to be missing with great frequency (Zankl and Zang, 1972). Other chromosomal abnormalities have also been detected in meningiomas by the same group of workers, with the intriguing demonstration, in three such tumours, of positive immunofluorescence against an SV-40-related tumour antigen (Weiss *et al.*, 1975) and morphological evidence of a papovavirus (Weiss *et al.*, 1976). Whether these findings, which need to be

confirmed and their significance assessed, indicate any relationship between these neoplasms and a known oncogenic virus has yet to be determined.

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 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. A similar case has been reported by Manuelidis (1971). This was in a 53-year-old woman who developed a left frontal glioblastoma at the site of the lobotomy scar 12 years after operation; the patient had suffered from schizophrenia for 26 years prior to lobotomy. 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. 169, 170, p. 231) of the right parietal lobe was successfully removed and who, 16 years later, was fully employed and without evidence of recurrence. 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. 169). 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 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. 67) 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. 29).

Infections and inflammations. In the perspective of present-day concepts on malignant transformation, which attribute increasing importance to modifications of the cell genome by oncogenic viral agents, the search for viral involvement in human neoplasia continues unabated (see Sanders, 1975, for an informative review). The implications inherent in the modern virus theories invoked in the possible pathogenesis of cancer and especially the modifications that must be brought in this regard to our concept of viruses as horizontal transmissible infective agents are critically and profitably discussed by Foulds (1975). In any event, it is agreed that at this time no human malignant neoplasm has so far been unequivocally demonstrated to be induced by a virus. Thus the occasional observation of virus-like particles in human brain tumours seems devoid of immediate aetiological significance, and the same is probably true of viral structures identified in experimental murine tumours induced with carcinogens (see below). On the other hand, in recent years the production of experimental tumours by oncogenic viruses has provided a valuable model for research, which will be reviewed on p. 14.

In the present context, considerable interest remains centred on the nature of the relationship between viral oncogenesis and *progressive multifocal leucoencephalopathy*. This degenerative demyelinating disease, in which the cytopathological features include, among others, the presence of giant atypical astrocytes with bizarre monstrous nuclei that have the characteristics of malignant cells, has now been established, on morphological (ZuRhein, 1969) and virological (Weiner and Narayan, 1974) grounds, to be caused by the replication, in glial cells, of virions belonging to the papova group of viruses. Significantly, a recent report describes the development of multiple gross and microscopic gliomatous nodules in the centres of the demyelinating lesions of such a case (Castaigne *et al.*, 1974). Also one of the strains of viruses causing the disease has proved to be oncogenic, resulting in the development of malignant neuroepithelial tumours in a large proportion of hamsters inoculated intracerebrally or subcutaneously after birth (see below, p. 15). Another strain of the same human papova group of viruses has moreover been shown to be capable of transforming human brain cells in culture (Santoli *et al.*, 1975). The neurooncogenic potential of this viral-induced neurological disease therefore seems to have been well demonstrated.

Mention is made elsewhere (p. 241) of observations in which gliomas have been found in association with the plaques of multiple sclerosis. The incidence of this association is so rare that its significance, if any, is obscure.

Alterations in immunological responses. As further detailed on p. 103, a significantly increased incidence of neoplasms, especially of the reticuloendothelial system, has been

recorded as a sequel of *organ transplantation.* The prevalence of central nervous system involvement has been stressed by Schneck and Penn (1971) and is generally attributed to the induced suppression of the immunological response combined with the relatively high immunological tolerance of the brain. Indeed, in transplant recipients there is a notable tendency for this organ to be the only one involved. The implications of such observations in respect of the relationship that may exist between disturbances of immunological mechanisms and tumour induction are being extensively debated today. See also our remarks below on the immunological mechanisms that may operate in the context of human gliomas (p. 17).

EXPERIMENTAL TUMOUR PRODUCTION

Chemical carcinogens

The production of intracranial tumours has been repeatedly achieved by experimental means. This aspect of neurooncology has been particularly fruitful in recent years and now commands a massive and ever-increasing literature. The discussion that follows must of necessity represent an incomplete survey of a still rapidly moving and expanding field.

Successful *oral* administration of 2-acetylaminofluorene was reported by Vazquez-Lopez (1945, 1 tumour) and by Hoch-Ligeti and Russell (1950, 3 tumours). Three of the neoplasms 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. One glioma was also obtained by Symeonides (1954). Twenty-five gliomas, mostly poorly differentiated, 2 malignant meningeal tumours, and 1 neurilemmoma have since been reported in a large series of rats of various strains fed with the same compound or with lead subacetate, the larger proportion of intracranial tumours being, however, obtained with the latter alone (Oyasu *et al.*, 1970). Using a combination of low-protein diet and spermicidal contraceptive cream administered either *per os* or *per vaginam*, Hoch-Ligeti (1957) produced 2 brain tumours, described as poorly differentiated astrocytomas. Malignant intracranial neurilemmomas and one medulloblastoma were also obtained by Snell *et al.* (1961) in rats fed with 2-7-acetylaminofluorene. 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 and mammary glands. The urinary bladder and the ear duct are also often involved, and lead subacetate feeding alone was found to result in a notable incidence of renal cortical neoplasms. 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 investigation, and studies on the hormonal dependence of experimentally-induced brain tumours obtained following the local implantation of carcinogenic hydrocarbons are referred to below. 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.

Attention should also be drawn to the findings of Szepsenwol (1969), who noted an appreciable number of frontal ganglioneuromas in mice fed for a long time on a diet supplemented by lecithin or cholesterol; these were well-differentiated neoplasms. Subsequent observations have also revealed two oligodendrogliomas in mice maintained on the same regimen (Szepsenwol, 1971).

N-nitroso compounds. The neurotropicity of these powerful resorptive carcinogens was first established by Druckrey and his co-workers (1965). Since then, they have been widely used for the production of an impressive variety of tumours of the central and peripheral nervous system. A considerable literature now covers this aspect of experimental oncology, which has been reviewed, among others, by Wechsler (Wechsler *et al.*, 1969; Wechsler, 1972), Druckrey *et al.* (1972), Koestner *et al.* (1972), and Jänisch and Schreiber (1974).

The type of tumours induced and the regularity with which they are obtained are variously dependent on the compound selected, the dose concentration, the animal species and strain, and the route of administration. Although other animals, such as the mouse, hamster and dog have also been used, the laboratory *rat*, in various strains, is the experimental animal of choice. The rabbit is also highly susceptible.

Although a large number of other resorptive alkylating agents have been employed for this purpose (see Jänisch and Schreiber), the most widely used of the nitroso compounds at this time are *methylnitrosourea* (MNU) and *ethylnitrosourea* (ENU). Neurotropicity is maintained whether the chemical is administered via the subcutaneous, intramuscular, intravenous, intraperitoneal, intracerebral or transplacental route, or by gastric absorption. Repeated *intravenous* injection of MNU to young adult rats results in neurogenic tumours in 97 per cent of animals (Swenberg *et al.*, 1972a). The highly successful and convenient *transplacental* method, leading to tumours in virtually 100 per cent of the offspring, is based on the administration of a single intravenous injection of ENU to gravid rats on the 15th or 16th day of gestation at a dose considerably lower than that needed to produce tumours in the adult (Ivankovic and Druckrey, 1968; Koestner *et al.*, 1971). A direct dose-response relationship has been determined (Swenberg *et al.*, 1972b).

Similar results have more recently been obtained by the daily intragastric administration of ethylurea combined with sodium nitrite in pregnant rats during the third week of their pregnancy. Since neither of the two chemicals produces neurogenic tumours on its own, the findings suggest that ENU is synthesised from these precursor substances under the influence of the gastric juice (Ramadan and Wechsler, 1975). The implications to be drawn from such experiments have yet to be assessed.

Multiple nervous system tumours, either of the same or of different cell types, are often obtained, even after a single exposure to the carcinogen. In the peripheral nervous system, the most frequently induced tumours are *Schwannomas* which exhibit various degrees of anaplasia depending on the compound used, the technique of administration, and the strain. The less differentiated examples are usually obtained following transplacental ENU in Sprague-Dawley or Long-Evans rats, whereas more differentiated Schwannomas are more often produced after repeated intravenous MNU injection in Fisher rats. The *trigeminal*

nerve root is the most frequently involved by growth, followed by the *spinal nerve roots*. Following transplacental induction with ENU, these neoplasms usually appear in the offspring after approximately 200 days. From electron microscopic examination of very early examples, their Schwann cell origin is well established even when they are most anaplastic, and their behaviour in vitro convincingly aligns them with the more differentiated Schwannomas found in man (Rubinstein *et al.*, 1976; Conley *et al.*, 1976).

The central nervous system tumours are almost all *gliomas*, whereas neoplasms of neuronal origin have been reported only exceptionally (Stroobandt and Brucher, 1968). Both the brain and the spinal cord are involved. After transplacental ENU, most of the gliomas appear in the offspring after approximately 300 days. Periventricular subependymal growths are frequent. The tumours are most often of mixed cell type, and their different cellular components cannot always be identified with certainty. Second in frequency are the oligodendrogliomas; this contrasts with the prevalence of astrocytomas obtained with various strains of RNA tumour viruses (see below), but good examples of astrocytomas can also be produced with N-nitroso compounds (Sipe *et al.*, 1974). The typical histological picture of glioblastoma is very uncommon in this model, and medulloblastomas have been obtained only exceptionally (see below). A notable finding is the production of olfactory neuroblastomas in rats following the repeated subcutaneous injection of nitrosopiperidine and nitrosopiperazine compounds (Druckrey *et al.*, 1972).

The special vulnerability of the central nervous system does not seem related to the factor of immunological tolerance, as administration of antilymphocytic serum to rats treated with MNU did not increase the incidence of nervous system tumours (Denlinger *et al.*, 1973).

The exact mode of action of the N-nitroso compounds is being actively investigated at this time. Their neurotropicity is generally thought to be due primarily to the guiding action of their urea radical, which facilitates their diffusibility into the nervous system, thus compensating for their instability as carcinogens; their small molecular weight and their lipid solubility may also play a part. Like other alkylating agents, they are both mutagenic and teratogenic, their action in each case being probably due to their alkyl radical, which results in the alkylation of one or more bases in the DNA chain. The precise molecular basis of neoplastic induction was at first the object of a good deal of uncertainty, but there is increasing evidence that a defect in the excision repair mechanism of one of the alkylated bases from brain DNA may underlie the process: apparently, the brain is specifically unable to eliminate the alkylated base guanine when the alkylation takes place at the o^6 position; anomalous base-pairing of the alkylated guanine with thymine then takes place, resulting in a stable but defective conformation of the DNA molecule (Goth and Rajewsky, 1974; Margison and Kleihues, 1975).

Whatever the mechanism of action of these substances, it is apparent that in transplacental carcinogenesis the rat nervous system is maximally sensitive to neoplastic transformation during the last days before birth and shortly thereafter. When given before or around the 12th day of gestation, ENU does not cause any nervous system tumours: its effects are solely toxic and teratogenic. The toxic effects are largely confined to the subependymal cells and to the external granular matrices (Bosch *et al.*, 1972). The subependymal cells of the cerebral hemispheres, as noted above, appear to be particularly susceptible also to neoplastic transformation, the target cells being almost certainly the still cycling spongioblasts in the course of their migration from the primitive ventricular zone. This vulnerability is presumably related to the fact that they are still mitotically active, which would agree with the generally accepted view that the agents act by interfering with DNA synthesis or repair mechanisms. The hypothesis would also account for the rarity of neuronal tumours in this model, although the almost total failure to obtain medulloblastomas remains an enigma.

An interesting departure from this rule was reported by Brucher and Ermel (1974), who described the occurrence of a neuroblastoma of the spinal cord parenchyma in a single offspring following the