TUMOURS OF NERVOUS SYSTEM

Speaking generally, tumours of the brain constitute a bleak but vitally important chapter of neurologic medicine. Their importance derives from the facts that they occur in great variety; produce numerous neurological symptoms because of their size, location, and invasive qualities; usually destroy the tissues in which they are situated and displace those around them; are a frequent cause of increased intracranial pressure; and, most of all, are often lethal. Slowly this dismal state of affairs is changing, however, thanks to advances in anesthesiology, stereotactic and microneurosurgical techniques, radiation therapy, and the use of chemotherapeutic agents.

INCIDENCE OF BRAIN TUMOURS AND THEIR TYPES

In 1993 there were estimated 400,000 deaths from cancer in the United States. Of these, the number of patients who died of primary tumours of the brain seems comparatively small (about 12,000), but in another 100,000 patients the brain was affected at the time of death (mainly by metastases). Thus, in approximately 25 % of all the patients with cancer, the brain and its coverings were involved by neoplasm at some time in the course of the illnes. Among causes of death from intracranial disease, tumour is exceeded in frequency only by stroke. In children, primary tumours of the brain represents 22 % of all childhood neoplasms, second in frequency after leukemia. In the United States population, the year-У incidence of all brain tumours is 46 per 100,000, and of primary tumours, 15 per 100,000. Excluding pituitary tumours, approximately 17,500 of primary brain neoplasms were diagnosed in 1993.

Revisions in the classification of intracranial tumours, utilizing recent refinements in the histopathologic study and the numerical grading system of Daumus — Duport and coworkers (known as the St. Anne-Mayo system), and the new classification of the Wo Health Organization, have resulted in the following amplification, The diffuse astrocytic tumours, the most common forms of g|i ma, have been subdivided into grade 2 astrocytoma, grade 3 anaplastic astrocytoma, and grade 4 glioblastoma multiform. These represent a spectrum in terms of growth potential (degree of nuclear atypia, cellularity, mitoses, and vascular changes) and prognosis. The rare grade 1 astrocytomas, which are difficult to distil guish from hamartomas, are omitted. Some of the glioblastomas with sarcomatous aspects (gliosarcomas) are so designated.

The pilocytic astrocytomas (tumours mostly of children and young adults), the pleomorphic xanthoastrocytomas (with lipidfilled cells), and the subependymal giant-cell astrocytomas (usually with tuberous sclerosis) have been set apart because of their different growth patterns, pathologic associations, and prognosis. The ependymomas are subdivided into cellular, myxopapillary. clearcell, and mixed types; the anaplastic myxopapillary tumour and the subependymoma are given a separate status.

The pathologic criteria of a malignant astrocytoma do not apply to oligodendroglioma, for reasons elaborated further on. Tumours derived from the choroid plexus are divided into two classes — papillomas and carcinomas. Meningiomas are classified on the basis of their cytoarchitecture and genetic origin into three catergories: the usual meningothelial or syncytial type, the anaplastic or malignant type, and atypical forms. Tumours of the pineal gland, which were not included in earlier classifications, comprise pineocytomas, pineoblastomas, and embryonal forms. The medulloblastoma is reclassified with the other tumours of a presumed neuroectodermal origin: the neuroblastomas, retinoblastomas, and ependymoblastomas. Tumours of the cranial and peripheral nerves are believed to differentiate into three types: schwannomas, neu rofibromas, and neurofibrosarcomas. The intracranial midline germ-cell tumours, such as germinoma, teratoma, choriocarcinoma. and endodermal sinus carcinoma have the given separate status. A miscellaneous group comprises lymphoma, hemangioblastoma, chordoma, hemangiopericytoma, spongioblastoma, and ganglioneuroma.

BIOLOGY OF BRAIN TUMOURS

Tumours would be exp $f_o$rm, he stated, at sites where there are rapid differentiations of germ layers and complex migrations of cells. Ribbert, in 1918, extended this hypothesis by postulating that the potential for differentiation of these stem cells would favor blastomatous growth. Also implicit in this histogenetic theory is the idea that the degree of anaplasia, or its opposite, differentiation, depends on the status of the cell rests. This Cohnheim — Ribbert theory seems to be most applicable to tumours that arise from vestigial tissues, such as craniopharyngiomas, teratomas, lipomas, and chordomas, some of which are more like hamartomas than neoplasms.

In recent years, thinking about the pathogenesis of primary brain tumours has been dominated by two main concepts: (1) the histogenic theory, which is based on the known or assumed embryology of nerve and glial cells and has remained the basis of most classifications of tumours of brain; and (2) the dedifferentiation theory, now generally accepted, that the tumours arise from neopiastic transformation of mature adult elements. A normal astrocytc. oligodendrocyte, microgliocyte, or ependymocyte is transformed into a neopiastic cell and, as it multiplies, the daughter cells become variably anaplastic, the more the higher the degree of malignancy.

The factor of age is important in the biology of brain tumours. Medulloblastomas, polar spongioblastomas (piloid astrocytomas), optic nerve gliomas, and pinealomas occur mainly before the age of 20 years, both meningiomas and glioblastomas are most frequent in the sixth decade.

Studies of the human genome have led to the identification of certain chromosomal rearrangements that are linked to tumours of the nervous system. In the fourth edition of the Catalog of Chroniosome Aberrations in Cancer, which lists 14,141 abnormal karyotypes, 550 are in tumours of the nervous system.

Based on the molecular genetic information cited above, our views of the pathogenesis of neoplasia are being cast along new lines. The specifics of these new data are presented in the following discussions of particular tumour types. The role of vjruses in the causation of tumours cannot be divorced from that of the genes, since viruses prove to be the most efficient mechanism for introducing a gene into tumour cells.

PATHOPHYSIOLOGY

The production of symptoms by tumour growth is governed h certain principles of physics and physiology. There, it was pointed out that the cranial cavity has a restricted volume, and the thro elements contained therein the brain (about 1400 ml), CSF Пл raL), and blood (150 ml) are relatively incompressible. According to the Monro — Kellie hypothesis, the total bulk of the three elements is at all times constant, and any increase in the volume of one of them must be at the expense of one or both of the others, A tumour growing in one part of the brain compresses and destroys brain tissue and displaces CSF and blood; once the limit of this accommodation is reached, the intracranial pressure (ICP) rises. The elevation of the ICP and perioptic pressure impairs axonal transport in the optic nerve and the venous drainage from the optic nerve head and retina, manifesting itself by papilledema.

It must be pointed out, however, that only some brain tumours cause papilledema while many others often quite as large do not. Thus one may question whether the Monro — Kellie hypothesis, and its simple implied relationships of intracranial volume and CSF pressure, adequately explains the development of raised TCP anu papilledema with brain tumours. In fact, in a slow process such as tumour growth, brain tissue is to some degree compressible, as one might suspect from the large indentations of brain produced by *m*eningiomas.

BRAIN DISPLACEMENTS AND HERNIATIONS

The problem of brain displacements and herniations is of vital importance in all mass lesions, and the underlying principles m be understood. Such phenomena become possible because the cranial cavity is subdivided into several compartments by sheets of relatively rigid dura (the falx cerebri, which divides the supratentorial space into right and left

halves, and the tentorium, which separates the cerebellum from the occipital lobes). The pressure from a mass within any one compartment, therefore, is not evenly distributed but causes shifts or herniations of brain tissue from one OIT1partment where the pressure is high to the other one where is lower. There are three well-known herniations, the *subfalcial, temporal lobe-tentorial,* and *cerebellar-foramen magnum,* as well as several less familiar ones (cerebellar-tentorial, diencephalic-sella turcica, and orbital frontal-middle cranial fossa). Herniation of swollen brain through an opening in the calvarium, in relation to craniocerebral injury or operation, is one more (transcalvarial)

Subfalcial herniation, in which the cingulate gyrus is pushed under the falx, occurs frequently, but little is known of its clinical manifestations. The most important herniation is the *temporal lobe-tentorial.* Here the medial part of one temporal lobe (uncus and parahippocampal gyrus) is displaced contralaterally and then forced into the oval-shaped tentorial opening through which the midbrain passes, The uncal hernia pushes the midbrain and subthalamus against the opposite free edge of the tentorial opening, exerting great pressure on the midbrain and subthalamus and on the vessels that encircle and enter these structures. The hemiparesis that results from compression of the cerebral peduncle by the tentorium is ipsilateral to the cerebral lesion and thus constitutes a false localizing sign. The extent to which the clinical disturbances attributed to uncal herniation are due to the compressive effects of the prolapse itself or to a lateral shift of central (diencephalic-mesencephalic) structures is controversial.

The *cerebellar-foramen magnum herniation* consists of downward displacement of the inferior mesial parts of the cerebellar hemispheres (mainly the ventral paraflocculi or tonsillae) through the joramen magnum, behind the cervical cord. The displacement may be bilateral or, in the case of a one-sided cerebellar lesion, unilateral. Bilateral displacement may result from a centrally placed callosal-frontal. Ufrontal tumour or from general swelling of the brain and is acompanied by downward displacement of the brainstem. It may also be accompanied by bilateral temporal lobe-tentorial herniations. The herniating cerebellar tissue may swell and become infarcted; but whether it does or not, the lethal effects of this herniation are the result of medullary compression.

The clinical manifestations of downward cerebellar are worse delineated than those of the temporal lobe-niation. Cushing considered the typical signs of cerebellar herniation to be episodic tonic extension and arching of the and extension and internal rotation of the limbs, w disturbances, cardiac irregularity (bradycardia or and loss of consciousness. Other signs with subacutely masses include pain in the neck, stiff neck, head tilt, paresth in the shoulders, dysphagia, and loss of tendon reflexes in the arms. It is important to determine which signs are due to the cerebellar herniation and which ones — to the attendant effects of ICP hydrocephalus. We would suggest that head tilt, stiff neck, arching of the neck, and paresthesias over the shoulders are attributable to the herniation, and that tonic extensor spasms of the limbs and body (so-called cerebellar fits) and coma are due to the compressive effects of the cerebellar lesion on medullary structures or of hydrocephalus on upper brainstem structures. Respiratory arrest is of the most danger and often a fatal effect of medullary compression occurs.

CLINICAL AND PATHOLOGICAL CHARACTERISTICS OF BRAIN TUMOURS

At the outset it should be stated that brain tumours may hardly exist with any symptoms. Often a slight bewilderment, siowness in comprehension, or loss of capacity for sustained mental activity is the only deviation from the norm, and signs of focal cerebral disease are wholly lacking. In some patients, on the other hand, there is early indication of cerebral disease in the form of a progressive hemiparesis, a seizure occurring in a previously healthy person or some other dramatic symptom, but until a scan is performed, the evidence may not be clear enough to confirm the agnosis of a cerebral tumour. The existence of a brain tumour be assumed because of the presence of increased intracranial P^r sure with or without localizing signs of the tumour. The symptoms are so definite that allows not only to diagnose an intracranial neoplasm but to fix particular region of its location as well. These localized growths may create certain syndromes seldom cause any other disease.

Changes in Mental Function

A lack of persistent application to everyday tasks, undue irritability, emotional lability, mental inertia, faulty insight, forgetfulness, reduced range of mental activity (judged by inquiring about the patient's introspections and manifested in his conversation), indifference to common social practices, lack of initiative and spontaneity all of which may incorrectly be attributed to worry, anxiety, *or* depression make up the mental abnormalities seen in this clinical case. Inordinate drowsiness, apathy, equanimity, or stoicism may be prominent features of this state. We have sought a convenient term for this complex of symptoms, which is the most common type of mental disturbance encountered in the neurological disease, but none seems entirely appropriate. There is both a reduction in the amount of thought and action and a slowing of reaction time. Much of this change in behavior is percieved by the patient with forbearance; if any complaint is made, it is of being weak, tired, or dizzy (nonrotational). Within a few weeks or months these symptoms become more prominent. When the patient is questioned, a long pause precedes each reply; sometimes the patient may not respond at all, or, at the moment, the examiner decides that the patient has not heard the question and prepares to repeat it, an appropriate answer is given, usually in few words. Moreover, the responses are often more intelligent than one would expect, considering the patient's torpid mental state. There are, in addition, patients who are overtly confused or demented. If the condition remains untreated, dullness and somnolence increase gradually and, finally, as increased intracranial pressure supervenes, the patient progresses to stupor or coma.

Headaches

These are an early symptom in about one-third of patients with brain tumour and are variable in nature. In some the pain is slight, dull in character, and episodic; in others it is severe and either dull or sharp but also intermittent. If there are any characteristic features of the headache, they would be its nocturnal occurrence or presence on first awakening and perhaps its deep nonpulsatile quality. However, these are not specific attributes, since migraine, hypertensive vascular headaches, etc., may also begin in the early morning hours or on awakening.

Vomiting

This symptom appears in a relatively small number of palients with a tumour syndrome of this type and usually accompanies the headache. It is more frequent with tumours of the posterior fossa. The most persistent vomiting (lasting several months), that we have observed was in a patient with a low brainstem glioma and in another with a subtentorial meningioma. Some patients may vomit unexpectedly and forcibly, without preceding nausea (projectile vomiting), but others suffer from both nausea and severe discomfort. Usually the vomiting is not related to the ingestion of food; often it occurs before breakfast.

Seizures

The occurrence of focal or generalized **seizures** is the other major manifestation of this group of cerebral tumours. They have been observed, in various series, in 20 to 50% of all patients with cerebral tumours. The occurrence of a seizure for the first time during adulthood is always suggestive of tumour. The localizing significance of seizure patterns has already been discussed. There may be one seizure or many, and they may follow the other symptoms or precede them for weeks or months or exceptionally, in patients with astrocytoma, oligodendroglioma, or meningioma within several years.

Regional or Localizing Symptoms and Signs

Sooner or later, in patients with psychomotor asthenia, headacheses, and seizures, focal cerebral signs will be discovered; some patients may have such signs. Nearly always, however, the focal gjgjvs are at first slight and subtle. Signs of increased intracranial pressure may become manifest at ive and establish the diagnosis of tumour even before focal or lateralizing signs are detectable. With the increase of CT or MRI practice the presence of a tumour will have been disclosed before either focal cerebral signs or the signs of increased intracranial pressure have become evident.

Glioblastoma Multiforme and Anaplastic Astrocytoma

These tumours account for about 20 % of all intracranial tumours, or about 55 % of all tumours of the glioma group, and for more than 90 % of gliomas of the cerebral hemispheres in adults. Although predominantly cerebral in location, these tumour types may be observed in the brainstem, cerebellum, or spinal cord. The peak incidence is in the middle adult age, but no age group is exempt. These tumours incidence in men is twice as much than in women.

The glioblastoma is highly malignant, infiltrates the brain extensively, and may attain enormous size before attracting medical attention. It may extend to the meningeal surface or the ventricular wall, which probably accounts for the increase in CSF protein (more than 100 mg/dL in many cases) as well as for an occasional pleocytosis of 10 to 100 cells or more, mostly lymphocytes. Malignant cells, carried in the CSF, may form distant foci on spinal roots or cause a widespread meningeal gliomatosis. Extraneural metastases, involving bone and lymph nodes, are very rare; usually they occur only after a craniotomy has been performed. About 50 % of glioblastomas occupy more than one lobe of a hemisphere or are bilateral; between 3 and 6 % show multicentric foci of growth.

The tumour has a variegated appearance, being a mottled gray, red, orange, or brown, depending on the degree of necrosis and presence of haemorrhage, recent or old. It is highly vascular, and in an arteriogram one can often see a network of abnormal vessels, mistaken at times for a hemangioma, and displacement of normal vessels as an effect of the tumour mass. Some part of one lateral ventricle is often distorted, and both lateral and third ventricles may be displaced contralaterally, that are demonstrated by CT and MRI.

The characteristic histologic findings are great cellularity with pleomorphism of **cells** and nuclear atypia; identifiable astrocytes with fibrils in combination with primitive forms in many cases; tumour giant cells and cells in mitosis; hyperplasia of endothelial cells of small vessels; and necrosis, haemorrhage, and thrombosis of vessels. The vasculature may undergo a **sarcomatous** transformation with a prominent **reticuJin** and collagen interstitium. Originally, the glioblastoma was thought to be derived from and composed of primitive embryonal cells, but it is now generally thought to arise through anaplasia of mature astrocytes. Currently, the favored terms are *glioblastoma multiforme* and *anaplastic **astrocytoma.*** The two tumours differ in their age of onset and response to treatment. The mean age of patients with glioblastoma is 56 years and of those

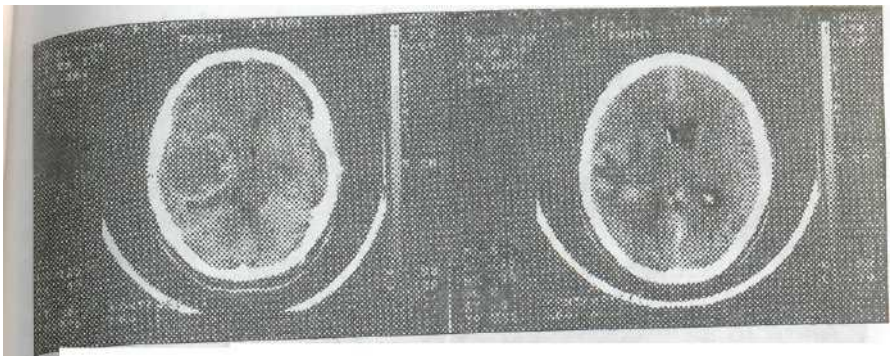


Fig- 30. CT. Anaplastic astrocytoma

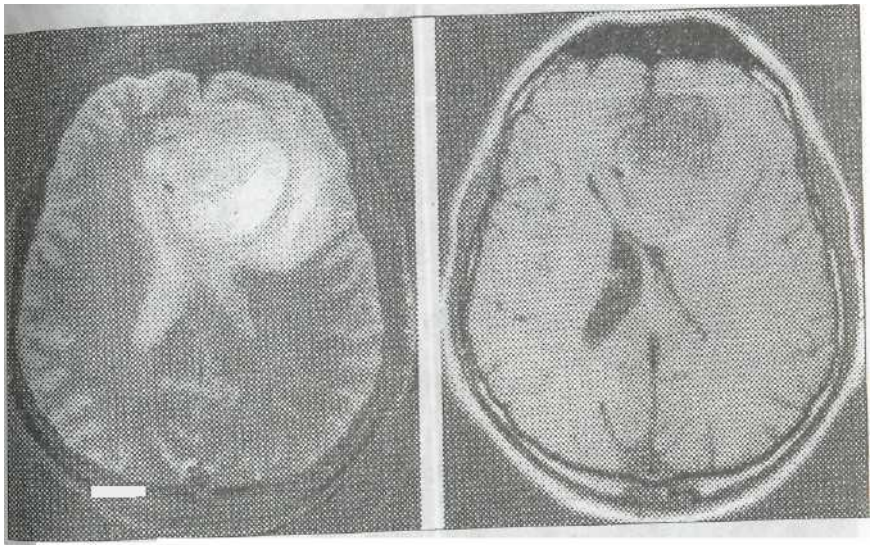


Fig. 31. MRI. Glioblastoma of the left frontal lobe

with anaplastic astrocytoma — 46 years. The 18-month postoperative survival was 15 % in patients with glioblastoma and 62 % in those with anaplastic astrocytoma. The prognosis is much better with astrocytoma grade 1 or 2.

Clinically, the diffuse cerebral symptoms and seizures (present in 30 to 40 % of cases) usually give way in a few weeks or months to a more definite frontal, temporal, parietooccipital, or callosal syndrome. However, do the symptoms and signs seldom point only to one lobe, and often one is satisfied to specify the general region of the hemisphere that is involved.

Astrocytoma

Grades 1 and 2 astrocytomas, which constitute between 25 and 30 % of cerebral gliomas, may occur anywhere in the brain or spinal cord. Favored sites are the cerebrum, cerebellum, hypothalamus, optic nerve and chiasm, and pons. In general, the location of

the tumour correlates to the age of the patient. Astrocytomas of the cerebral hemispheres arise mainly in adults in their third and fourth decades; astrocytomas in other parts of the nervous system are more frequent in children and adolescents. Cerebral astrocytoma is a slowly growing tumour of infiltrative character with a tendency to form large cavities or pseudocysts.

Other tumours of this category are noncavitating, grayish white, firm, and relatively avascular, almost indistinguishable from normal white matter, with which they merge imperceptibly. r cium may be deposited in parts of the tumour and be seen in scans.

The CSF is acellular, and the only abnormalities in some case are the increased pressure and protein content. The tumour distort the lateral and third ventricles and displace the anterior middle cerebral arteries. Microscopically, most tumours are posed of well-differentiated astrocytes of fibrillary type. gemistocytic *(gemistos* means "filled") types are less frequent ar have perhaps a worse prognosis. Many cerebral astrocytom. present as mixed astrocytomas and glioblastomas. The tumour cells contain glial fibrillary protein.

In about half the patients with astrocytoma, the opening symptom is a focal or generalized seizure, and between 60 and 75 % of patients have recurrent seizures in the course of their illness. The onset of focal seizures in individuals from 20 to 60 years of age should always arouse suspicion of a cerebral astrocytoma. Other subtle cerebral symptoms follow after months, sometimes after years. Headaches and signs of increased intracranial pressure are relatively late signs.

Temporal lobe gliomas in which mental symptoms precede seizures give rise to particular difficulty in diagnosis. Slight character and personality changes, moodiness, and episodes suggestive of schizophrenia may precede or follow the onset of temporal lobe seizures. In frontal gliomas, hemiparetic signs may consist of only a slight drift of the outstretched arm, a mild limp, and enhanced tendon reflexes; they may remain slight

in degree for a long time. Also, language difficulties and sensory changes are frequently slight and subtle. Seizures, headaches, and the mental symptoms described above may be present for several years, in some instances for 10 years or even longer, before the diagnosis is made.

In children the tumour is usually in the cerebellum and declares itself by some combination of gait unsteadiness, unilateral ataxia, and increased intracranial pressure (headaches, vomiting). In contrast to glioblastoma, the average survival period after the first symptom is 67 months in cerebral astrocytomas and 89 months in cerebellar ones.

Excision of part of the cerebral astrocytoma, particularly the cystic part, may allow survival in a functional state for many years. The cystic astrocytoma of the cerebellum is particularly benign. About 10 % of patients are alive and well as long as 20 to 30 years after excision of the cyst. In such cases, resection of the tumour nodule is of particular importance in preventing a recurrence. The role of radiation therapy is still controversial.

A survey of these lower grade resected tumours showed an improvement in 10-year survival after operation from 11 to 40 % if 5,300 cGy was given postoperatively. It also appears that seizure control is improved after radiation. In younger patients, particularly if the neurological examination is normal or nearly so, radiation can be delayed and the course of the tumour evaluated by frequent scans. An increase in seizures or worsening neurological signs then presses one to turn to radiation or further surgery. The reason for delaying radiation in younger patients is to avoid the dementia and hypopituitarism that it sometimes produces. Gen), tocytic tumours, however, generally do better with radiation. \, peated operations prolong life in some patients, but chemotheran has not occupied a definite place in the treatment of low-grade % trocytomas yet. The tumours with an oligodendroglial сотропец may respond to the combination chemotherapy that is used for an. aplastic oiigodendroglioma as discussed below.

Oligodendroglioma

The tumour is derived from oligodendrocytes or their precursor cells and may be identified at any age, most often in the third and fourth decades, with an earlier peak at 6 to 12 years. It is relatively infrequent, constituting about 5 to 7 % of all intracranial gliomas. Males outnumber females in the ratio 2:1. In some cases the tumour may be recognized macroscopically because of its pink-gray color and multilobular form, its relative avascularity and firmness (slightly tougher than surrounding brain), and its tendency to encapsulate and form calcium and **small** cysts. Most oligodendrogliomas, however, are grossly indistinguishable from other gliomas. This type of cell has a small, round nucleus and a halo of unstained cytoplasm ('Tried egg" appearance). The cell processes are few and stubby, visualized only with silver carbonate stains. Some of the gliofibrillary oligodendrocytes have intense immunoreactivity to **glial fibriilary** acidic protein, similar to normal my elm-forming oligodendrocytes. Microscopic calcifications are observed frequently, mainly in relation to zones of necrosis. Probably half the tumours generally classified as oligodendrogh'omas are in fact mixed types (oligodendroglioma-astrocytoma), which seem to have a better prognosis than pure **astrocytoma.**

The most common sites of this tumour are the frontal and temporal lobes (40 to 70 %), often deep in the white matter, with a streak of calcium but little or no surrounding edema. Sometimes the tumour presents in a lateral ventricle. Rarely it occurs in other parts of the nervous system. By extending to the pial surface or ependymal wail, the tumour may metastasize distantly in ventricu-losubarachnoid spaces, accounting for 11 % of gliomas with me-ningeal dissemination (less frequent than medufloblastoma and giioblasloma). The tumour does not lend itself to the glioma grading scale, but malignant degeneration, evidenced by greater cellularity and by numerous and abnormal mitoses, and endothelial proliferation occur in about a third of the cases. Such tumours are Sines called oligodendroblastomas.

The typical oligodendroglioma grows slowly. As with astrocytomas the first symptom in more than half the patients is a focal or generalized seizure; seizures often persist for many years before other symptoms develop. Approximately 15 % of patients enter the hospital with early symptoms and signs of increased intracranial pressure and even a smaller number with focal cerebral signs (hemiparesis). Much less frequent findings are unilateral extrapyramidal rigidity, cerebellar ataxia, Parinaud syndrome, intratumoural haemorrhage, and meningeal oligodendrogliosis (cranial-spinal

nerve palsies, hydrocephalus, lymphocytes in CSF). Calcium is seen in CT scans in more than half the cases.

Surgical excision followed by radiation therapy has been the conventional treatment for oligodendroglioma. However, because f uncertainty as to the histologic classification of many of the reported cases, it is not clear whether radiation therapy prolongs survival. Well-differentiated oligodendrogliomas should probably not receive radiation. Mixed oligodendrogliomas and astrocytomas should be treated like astrocytomas. Many *anaplastic oligodendro gliomas,* both newly discovered and recurrent ones, respond impressively to chemotherapeutic agents, particularly to PCV a comoirmtion of procarbazine, lomustine (CCNU), and vincristine given in approximately 6 cycles.

Ependymoma

Ependymomas are derived from differentiated ependymal cells, i.e., the cells lining the ventricles of the brain and the central canal I of the spinal cord. As one might expect, the tumours grow either into the ventricle or adjacent brain tissue. The most common cerebral site is the fourth ventricle; in the spinal cord, most ependymomas originate in the Iumbosacral regions, many from the conus or filum terminale. Grossly, those in the fourth ventricle are grayish pink, firm, cauliflower-like growths; those in the cerebrum, arising from the wall of the lateral ventricle, may be large (several centimeters in diameter), reddish gray, and softer and more clearly demarcated from adjacent tissue than astrocytomas, but they are not encapsulated. The tumour cells tend to form canals (rosettes) or circular arrangements around blood vessels (pseudorosettes). Some ependymomas, called epithelial, are densely cellular and anaplastic; others are better differentiated and form papillae. Some of the well-differentiated fourth ventricular tumours are probably derived from subependymal astrocytes.

Anaplastic ependymomas are identified by their high mitotic activity and endothelial proliferation, nuclear atypia, and necrosis. Some, in young children, are called *ependymoblastomas.* The correlations between histopathologic features and clinical outcomes have not been well defined.

Approximately 6 % of all intracranial gliomas are of this type; the percent age is higher in children (8 %). About 40 % of the infratentorial ependymomas occur in the first decade of life, a few as early as the first year. The supratentorial ones are more evenly distributed among all age groups, but in general the age incidence is lower than in malignant gliomas.

The *symptomatology* depends on the location of the growth. The clinical manifestations of fourth ventricular tumours (the most common intracranial site) are described further on in this chapter. Cerebral ependymomas resemble the other gliomas in their clinical expression. Seizures occur in approximately one-third of the cases. The interval between the first symptom to operation ranges from 4 weeks, in the most malignant types, to 7-8 years. Doubtless the prognosis depends on the degree of anaplasia. Surgical removal is supplemented by radiation therapy, particularly to address the high rate of seeding of the ventricles and spinal axis. In the treatment of cerebral ependymoblastomas, antitumour drugs are often used in combination with radiation therapy.

Meningioma

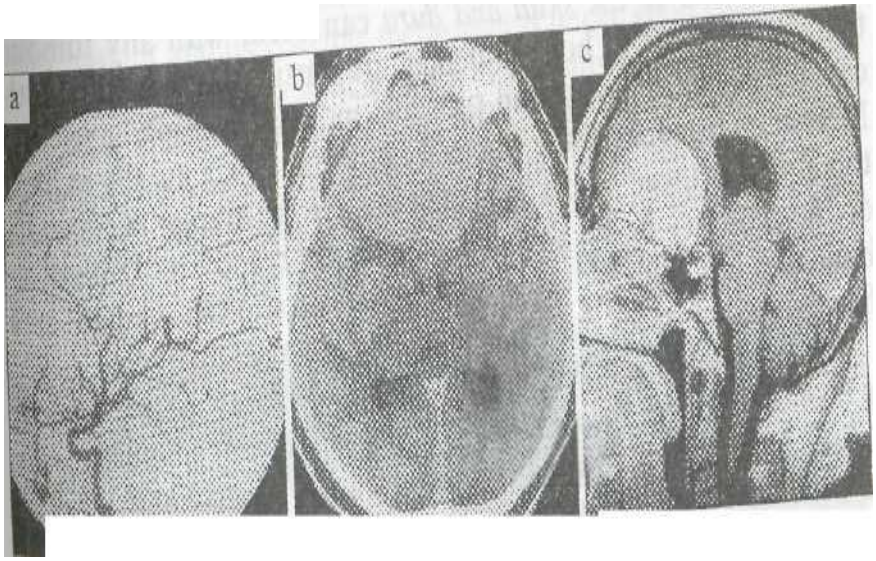
This is a benign tumour originating from the dura mater or rachnoid. Meningiomas represent about \5 % of all primary intracranial tumours; they are more common in women than in men (2:1) and have their highest incidence in the seventh decade. Some are familial. There is evidence that persons who have undergone radiation therapy to the scalp or cranium are particularly vulnerable to the development of rneningiomas and that the tumours appear at an earlier age. Many meningiomas are associated with a karyotype abnormality, a loss of one chromosome 22.

Meningiomas may arise from dural fibroblasts, or, more commonly, from arachnoidal (meningothelial) cells, in particular from those forming the arachnoid villi. Since the clusters of arachnoidal cells penetrate the dura in largest number in the vicinity of venous sinuses, these are the sites of predilection. Grossly, the tumour is firm, gray, and sharply circumscribed, and it takes the shape of the space in which it grows; thus, some tumours

are flat and plaquelike, others arc round and lobulated. They may indent the brain and acquire a piaarachnoid covering as part of their capsule, but they are always clearly demarcated from the brain tissue (extraaxial). Rarely, they arise from arachnoidal cells within the choroid plexus, forming an intraventricular meningioma. Microscopically, the cells are relatively uniform with round or elongated nuclei, visible cytoplasmic membrane, and a characteristic tendency to encircle one another, forming whorls and *psammoma bodies* (laminated calcific concretions). Currently neuropathologists recognize the meningothelial (syncytial) form as being the most common. It is readily distinguished from other nonmeningothelial tumours such as hemangiopericytomas, fibroblastomas, chondrosarcomas, etc.

The usual sites are the sylvian region, superior parasagittal surface of the frontal and parietal lobes, olfactory groove, lesser wing of the sphenoid bone, tuberculum sellae, superior surface of the cerebellum, cerebellopontine angle, and spinal canal. As much they extend to the dural surface, they often invade and erode the cranial bones or excite an osteoblastic reaction. Sometimes they give ri**se** to an exostosis on the external surface of the skull.

Fig. 38. Meningioma of the rhinoolfactonus fossa



Metastatic Carcinoma

Among secondary intracranial tumours, only metastatic carcinoma occurs with high frequency. The pathophysiology of meta. static carcinoma is the complex of biologic mechanisms that gov-ern the detachment of tumour cells from the primary growth, their transport to distant tissues, their implantation on the capillary en-dothelium of the particular organ in which they will eventually grow.

Autopsy studies disclose intracranial metastases in approximately 25 % of patients who die of cancer. About 80 % of the metastases are in the cerebral hemispheres and 20 % in posterior fossa structures, proportions that correspond roughly to the weight of these portions of the brain and their blood flow.

Metastases to the skull and dura can occur with any tumour that metastasizes to bone, but they are particularly common with carcinoma of the breast and prostate and with multiple myeloma. Metastatic tumours of the convexity of the skull are usually asymptomatic, but those at the base may involve the cranial nerve roots or the pituitary body. Bony metastases are readily recognized on bone and CT scans. A carcinoma metastasizes to the subdural surface and compresses the brain, like a subdural haematoma.

Carcinomas reach the brain by hematogenous current. Almost a third of them originate in the lung and half this number in the breast; melanoma is the third most frequent source, and the gastrointestinal tract (particularly the colon and rectum) and kidney are the next most common. Carcinomas of the gallbladder, liver, thyroid, testicle, uterus, ovary, pancreas, etc., account for the remainder. Carcinomas of the prostate, esophagus, oropharynx, and skin (except for melanoma) almost never metastasize to the substance of the brain. From a somewhat different point of view, certain neoplasms are

particularly prone to metastasize to the brain, 75 % of melanomas do so, 57 % of testicular tumours, and 35 % of bronchial carcinomas, 40 % of which are small-cell tumours. The cerebral metastasis is solitary in 47 % of cases, a somewhat high-^figure than that observed in our practice and reported by others.

Generally the cerebral metastasis forms a circumscribed mass, solid but sometimes in the form of a ring (i.e., cystic), and rather little glial reaction but much regional vasogenic edema. Metastases from chorioepithelioma and melanoma are likely be haemorrhagic, and some from the lung and kidney may be haemorrhagic as well.

The usual clinical picture in *metastatic carcinoma of the brain* does not differ from that of glioblastoma multiforme. Headache, focal weakness, mental and behavioral abnormalities, seizures, ataxia, aphasia, and signs of increased intracranial pressure all inexorably progressive over a few weeks or months are the common clinical manifestations.

CT scanning, with and without contrast, will detect practically all sizeable (>1 cm) metastases. MRI will, in addition, expose associated leptomeningeal disease and is more sensitive to small cerebellar deposits.

In patients with a single parenchymatous metastasis, surgical extirpation should be undertaken provided that growth of the primary tumour and its systemic metastases is under good control and the cerebral metastasis is accessible to the surgeon and is not located in a strategic motor or language area of the brain; usually excision is followed by radiation therapy. Systemic chemotherapy has been thought to be ineffective against cerebral metastases. ltnmunotherapy has not been widely employed yet.

Despite these therapeutic measures, survival is only slightly prolonged. The average period of survival, even with therapy, is about 6 months. Between 15 and 30 % of patients live for a year the to 10 % for 2 years; with certain radiosensitive tumours (lymphl ma, testicular carcinoma, choriocarcinoma, some breast cancers), survival may be much longer.

Medulloblastoma

The medulloblastoma is a rapidly growing embryonic tumour that arises in the posterior part of the cerebellar vermis and neuroepithelial roof of the fourth ventricle in children. It rarely occurs in the cerebellum or other parts of the brain in adults.The tumour frequently fills the fourth ventricle and infiltrates its floor. Seeding of the tumour may occur on the ependymal and meningeal surfaces of the cisterna magna and around the spinal cord. The tumour is solid, gray-pink in color, and fairly well demarcated from the adjacent brain tissue. It is very cellular, and the cells are small and closely packed with hyperchromatic nuclei, little cytoplasm, many mitoses, and a tendency to form clusters or pseudorosettes. The majority of the patients are children from 4 to 8 years of age, and males outnumber females in the ratio 3:2 or 3:1 in the many reported series. As a rule, symptoms have been present for 1 to 5 months before the diagnosis is made. The clinical picture is distinctive. Typically, the child becomes listless, vomits repeatedly, and has a morning headache. The first diagnosis that suggests itself may be gastrointestinal disease or abdominal migraine. Soon, however, a stumbling gait, frequent falls, and squint lead to a neurological examination and the discovery of papilledema. The latter is present in all the patients except a small proportion of those with the tumour located laterally in the cerebellum, as it usually is in adults. Dizziness (positional) and nystagmus are frequent.

Ependymoma and Papilloma of the Fourth Ventricle

Ependymomas, as pointed out earlier in this chapter, arise from he walls of the ventricles. About 70 % of them originate in the fourth ventricle. Postmortem, some of these tumours, if small, are found protruding into the fourth ventricle, never having produced symptoms. Whereas the incidence of supratentorial ependymomas is spread

evenly throughout life, the fourth ventricular ependymomas occur mostly in childhood. Males have been affected almost twice as often as females.

Ependymomas usually arise from the floor of the fourth ventricle, extend through the foramina of Luschka and Magendie, and may invade the medulla. These tumours produce a clinical syndrome much like that of the medulloblastoma except for their more protracted course and lack of early cerebellar signs. Symptoms may be present for 1 or 2 years before diagnosis and operation. About two-thirds of the patients come to notice because o increased intracranial pressure; in the remainder, vomiting, difficulty in swallowing, paresthesias of the extremities, abdominal rain, vertigo, and head tilt are prominent manifestations. Surgical removal offers the only hope of survival. The addition of radiation therapy and sometimes ventriculoperitoneal shunting of CSF prolong life.

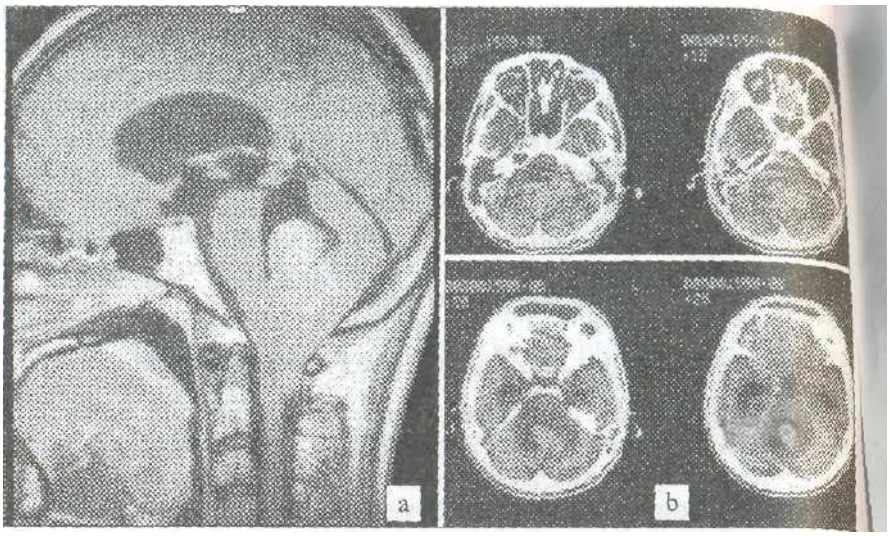


Fig. 40. Ependymoma, a) MR I. b) CT

An oncogene T (tumour) antigen of the SV40 virus is possibly involved in tumour induction. Essentially these are tumours of the childhood period. Entirely 50 % of the tumours cause symptoms in the first year of life and *15* % in the first decade. In the younger patients, hydrocephalus **is** usually the presenting syndrome, often aggravated acutely by haemorrhage; there may be papilledema, an unusual finding in a hydrocephalic child. Headaches, lethargy, stupor, spastic weakness of legs, unsteadiness of gait, and diplopia are more frequent in the older child. Sometimes patients present with a syndrome of the cerebellopontine angle, where the tumour presumably arises from choroid plexus that projects into the lateral recess. *One* consequence of the tumour is thought to be increased CSF formation, which contributes to the hydrocephalus. Some of the tumours acquire more malignant attributes (mitoses, atypia of nuclei, and invasion of surrounding brain). They have the appearance of a carcinoma and may be mistaken for an epithelial metastasis from an extracranial site.

Treatment is by surgical excision, but palliative ventricular shunting may be needed first if the patient's condition does not permit surgery. The prognosis of choroid plexus carcinomas is poor.

Hemangioblastoma of the Cerebellum

This tumour is also referred to in connection with von Hippel — Lindau disease. Dizziness, ataxia of gait or of the limbs on one side symptoms and signs of increased intracranial pressure from compression of the fourth ventricle, and in some instances an associated retinal angioma or hepatic and pancreatic cysts (exposed by MRl) constitute the syndrome. There is a tendency later to develop malignant renal or adrenal tumours. Many patients have polycythemia due to elaboration of an erythropoietic factor by the tumour.

The age of onset is between 15 and 50 years. Blacks, whites, d Asians are equally affected. Dominant inheritance is well known. In cases associated with renal-cell carcinoma and pheochromocytoma a defect localized in so called a tumour suppressor gene on chromosome 3.

The diagnosis can be surmised from the appearance on MRI of a cerebellar cyst containing an enhancing modular lesion on its wall. Often the associated retinal hemangioma will be disclosed by e same imaging procedure. The angiographic picture is also characteristic: a tightly packed cluster of small vessels forming a mass >f 1.0 to 2.0 cm in diameter. Craniotomy with, opening of the cerebellar cyst and excision of the mural hemangioblastomatous nodule may be curative. There is a high rate of recurrence if the entire tumour, including the nodule, is not completely removed. The lesion successfully removed in 80 % of patients, 50 %, in whom an isolated cerebellar lesion had apparently been resected completely, developed recurrent tumours. A retinal hemangioblastoma may be the initial finding and may lead to blindness if not treated by laser beam. The children of a parent with a hemangioblastoma of the cerebellum should be examined regularly for an ocular lesion and renal cell carcinoma (another complication).

Pinealoma

There has been much uncertainty as to the proper classification of pineal tumours. Originally they were all thought to be composed of pineal cells, hence true pinealornas. Today four types are recognized: the germinoma (atypical teratoma), the pinealoma (pineocytoma and pineoblastoma), the true teratoma with cellular derivatives of all three germ layers, and the glioma.

The *germinoma* is a firm, discrete mass that usually reaches 3 to 4 cm in the greatest diameter. It compresses the superior colliculi and sometimes the superior surface of the cerebellum and narrows the aqueduct of Sylvius. Often it extends anteriorly into the third ventricle and may then compress the hypothalamus. A minoma may also arise in the floor of the third ventricle; this been referred to as an ectopic pinealoma or *suprasellar ma.* Microscopically, these tumours are composed of large, spherical epithelial cells separated by a network of reticular connective tissue, which contains many lymphocytes.

The *pineocytoma* and *pineoblastoma* reproduce the normal structure of the pineal gland. These tumours enlarge the gland, are locally invasive, and may extend into the third ventricle and seed along the neuraxis. Their growth characteristics resemble those of the germinoma. Cytologically, the pineocytoma is a moderately cellular tumour with no histologic attributes of anaplasia. The tumour cells tend to form circular arrangements, so-called pineocytomatous rosettes. Pineocytes may be impregnated by silver carbonate methods and some contain the retinai S antigen of photoreceptor cells. Pineoblastomas are highly cellular and composed of small-undifferentiated cells bearing some resemblance to medulloblasts**.** The *teratoma* and *dermoid* and *epidermoid cysts* have no special features some are quite benign. The *gliomas* have the usual morphologic characteristics of an astrocytoma of varying degrees of malignancy. Of the four groups of pineal tumours, approximately 50 % are germinomas. True teratomas and gliomas are relatively infrequent. Children, adolescents, and young adult males are affected more than females.

In some cases, the clinical syndrome of the several types of pineal tumours consists solely of symptoms and signs of increased intracranial pressure. Besides, the most characteristic localizing signs are an inability to look upward and slightly dilated pupils that react on accommodation but not to light (Parinaud syndrome). Sometimes ataxia of the limbs, choreic movements, or spastic weakness appear in the later stages of the illness. It is uncertain whether the ocular and motor signs are due to neoplastic compression of the brachia conjunctiva and other tegmental structures of the upper midbrain or to

hydrocephalus (dilation of the posterior part of *the* third ventricle). Probably both mechanisms are operative. Precocious puberty occurs in males who harbor a germinoma. Diagnosis is made by CT and MRI (Fig. 41). The CSF may contain tumour cells and lymphocytes.

These lesions were formerly judged to be inoperable. However, the use of the operating microscope now makes it possible to excise these tumours by a supracerebellar or transtentorial approach.

The use of chemotherapy in addition to or instead of cranial irradiation is being evaluated. Several of our patients have survived more than 5 years after the removal of pineal gliomas.

Tumours of the Third Ventricle

The most important of these is the colloid tumour, which is derived, it is generally believed, from ependymal cells of a vestigial third ventricular structure known as the paraphysis. The cysts vary in size from 1 to 4 cm in diameter, are oval or round with a smooth external surface, and are filled with a glairy, gelatinous material containing a variety of mucopolysaccharides. The wall is composed of a layer of epithelial cells, some ciliated, surrounded by a capsule of fibrous connective tissue. Although congenital, the cysts practically never declare themselves clinically until adult life, when they block the third ventricle and produce an obstructive hydrocephalus.

This tumour should be suspected in patients with intermittent severe bifrontal-bioccipital headaches, sometimes modified by posture ("ball valve" obstruction of the third ventricle) or with crises of headache and obtundation, incontinence, unsteadiness of gait, bilateral paresthesias, dim vision, and weakness of the legs with sudden falls but no loss of consciousness *("drop attacks").* Stooping has resulted in an increase or onset of headache and loss of valance. However, this intermittent obstructive syndrome has been '"frequent in our experience. More often the patient has no headache but the symptoms of normal-pressure hydrocephalus.

The treatment for many years has been surgical excision satisfactory results have also been obtained by ventriculoperitoneal shunting of the CSF, leaving the benign growth untouched. Decompression of the cyst by aspiration under stereotaxic control has become an increasingly popular procedure.

Other tumours found in the third ventricle and giving rise mainly to obstructive symptoms are craniopharyngiomas, papillomas the choroid plexus, and ependymomas.

Craniopharyngioma

This is a histologically benign epithelioid tumour, generaily assumed to originate from *cell rests* (remnants of Rathke's pouch) at the junction of the infundibular stem and pituitary. By the time the tumour has attained a diameter of 3 to 4 cm, it is almost always cystic and partly calcified. Usually it lies above the sella turcica, depressing the optic chiasm and extending up into the third ventricle. Less often it is subdiaphragmatic, i.e., within the sella, where it compresses the pituitary body and erodes one part of the wall of the sella or a clinoid process; seldom does it balloon the sella like a pituitary adenoma. Large tumours may obstruct the flow of CSF. The tumour is oval, round, or lobulated and has a smooth surface. The wall of the cyst and the solid parts of the tumour consist of cords and whorls of epithelial cells (often with intercellular bridges and keratohyalin) separated by a loose network of stellate cells. The cyst contains dark albuminous fluid, cholesterol crystals, and calcium deposits; the calcium can be seen in plain films or CT scans of the suprasellar region in 70 to 80 % of cases. The sella beneath the tumour tends to be flattened and enlarged. The majority of the patients are children, but the tumour is not infrequent in adults, and some of patients have been up to the age of 60.

The presenting syndrome may be one of increased intracranial pressure, but more often it takes the form of a combined pituitaryhypothalamic-chiasmal derangement. The symptoms are often subtle and of long standing. In children, visual loss and diabetes insipidus are the most frequent findings, followed by adiposity, delayed physical and mental development (Froehlich or Lorain syndrome), headaches, and vomiting. The visual disorder takes the form of dim vision, chiasmal field defects, optic atrophy, and papilledema. In adults, who outnumber children in the ratio 3:1, waning libido, amenorrhea, slight spastic weakness of one or both legs, headache without papilledema, failing vision, and mental dullness and confusion are the usual manifestations. Later, drowsiness, ocular palsies, diabetes insipidus, and disturbance of temperature regulation ndicating hypothalamic involvement may occur.

Modern neurosurgical techniques, reinforced by corticosteroid herapy before and after surgery, and careful control of temperature and water balance postoperatively permit successful excision of ill or part of the tumour in the majority of cases. When complete removal is attempted, the mortality rate ranges from 5 to 10 %. Stereotaxic aspiration is sometimes a useful palliative procedure, as are radiation therapy and ventricular shunting in patients with solid, nonresectable tumours.

Acoustic Neuroma

Approximately 3,000 new cases of acoustic neuroma are diagnosed each year in the united States (incidence rate of 1 per 100,000 per year). The tumour occurs occasionally as part of von Recklinghausen neurofibromatosis, in which case it takes one of two forms. Schwannomas are distinguished from neurofibromas (composed of both Schwann cells and fibroblasts) found in peripheral nerves of type 1 von Recklinghausen's disease. A small percentage of neurofibromas become malignant, a phenomenon that is highly unusual in schwannomas.

The usual acoustic neuroma in adults presents as a solitary tumour. Being a schwannoma, it originates in nerve. The examination of small tumours reveals that they practically always originate on the vestibular division of the eighth nerve just within the internal auditory canal. As the eighth nerve schwan it extends into the posterior fossa to occupy the angle. In this lateral position it is so situated as to com seventh, fifth, and less often the ninth and tenth cranial which are implicated in various combinations. Later it H and compresses the pons and lateral medulla and obstructs circulation. The highest incidence is in the fifth and sixth age decades, and the sexes are equally affected. Familial occurrence only the tumours that are part of von Recklinghausen's disease.

Usually, by the time of the first neurological examination, the clinical picture was quite complex. One-third of the patients w troubled by vertigo associated with nausea, vomiting, and pressor in the ear. The vertiginous symptoms resembled those of Meniere disease but differed in that discrete attacks separated by periods of normalcy were rare. The vertigo coincided more or less with hearing loss and tinnitus (most often a unilateral high-pitched ringing, sometimes a machinery-like roaring or hissing sound, like a kettle). By then, many of the patients were also complaining of unsteadiness, especially on rapid changes of position (e.g., in turning), and this may have interfered with work and other activities. Some of our patients ignored their deafness for many months or years; often the first indication of the tumour in such patients has been their need to use the unaccustomed ear for the telephone. Others neglected these symptoms to a point where they presented with impaired mentation, imbalance, and sphincteric incontinence. Hearing loss, slight facial weakness, and numbness of a cheek were then the only clinical findings that permitted an acoustic neuroma to be distinguished from some other cause of normal-pressure hydrocephalus.

The contrast-enhanced CT scan will detect practically all acoustic neuromas that are larger than 2.0 cm in diameter and project further than 1.5 cm into the cerebellopontine angle. Much smaller intracanalicular tumours can be detected reliably by MR1 with gadolinium enhancement, a procedure that should be performe patients suspected of harboring this tumour. Audiologic and vestibular evaluation includes the tuning fork tests, pure tone and speech audiometry, auditory fatigue and recruitment brainstem evoked responses, and vestibular tests. In combination, they permit localization of the deafness and vestibular disturbance to the cochlear and vestibular nerves rather than their end organs.

The CSF protein is raised in two-thirds of the patients (100 ml/dL in one-third) and a clinically inevident acoustic schwannoma is one of the causes of an unexpectedly high CSF protein when a lumh puncture is performed for other reasons.

The treatment is surgicai excision. Many neurosurgeons who have had the largest experience with these tumours favor the microsurgical suboccipital transmeatal operation. Small tumours can be removed safely by the translabyrinthine approach if no attempt is to be made to save hearing. With focused gamma or p_{ro}, ton radiation, the growth of many of the smaller tumours can be controlled. This approach is favored in older patients.

Neurinoma or schwannoma of the trigeminal (gasserian) ganglion or neighboring cranial nerves and meningioma of the cerebellopontine angle may in some instances be indistinguishable from an acoustic neuroma. They should always be considered if early deafness, tinnitus, and lack of response to caloric stimulation ("dead labyrinth") are not the initial symptoms of the cerebellopontine angle syndrome. A true cholesteatoma (epidermoid cyst) is a relatively rare tumour that is most often located in the cerebellopon-

tine angle, where it may simulate an acoustic neuroma but usually causes more severe facial weakness.

Pituitary Adenomas

Tumours arising in the anterior pituitary are of considerable interest to neurologists because they often cause visual and other symptoms related to involvement of structures bordering upon the sella turcica. Pituitary tumours are age-linked; they become increasingly numerous with each decade; by the eightieth year, small adenomas are found in more than 20 % of pituitary glands. In some cases, an apparent stimulus to adenoma formation is end-organ failure, as occurs, for example, with ovarian atrophy that induces a basophilic adenoma. Only a small proportion enlarge the sella, and these account for 6 to 8 % of pituitary tumours listed in all large series of intracranial neoplasms.

Adenomas of the pituitary are most often composed of chromophobe cells *(4* to 20 times as common as acidophil-cell adenomas): the incidence of basophil-ceil adenomas is uncertain. Histologic study is now based on immunoperoxidase staining techniques and is concerned with defining the nature of the hormones within the pituitary cells both of the normal gland and of pituitary adenomas. These methods have shown that either a chromophobe or an acidophil cell may produce prolactin, growth hormone *(LH),* and thyroid-stimulating hormone (TSH), whereas the basophil cells produce adrenocorticotropic hormone (ACTH), lipotropin, luteinizing hormone (LH), and follicle-stimulating hormone (FSH).

The development of sensitive (radioimmunoassay) methods for surement of pituitary hormones in the serum has made possible the detection of adenomas at an early stage of their development and the designation of several types of pituitary adenomas on the basis of the endocrine disturbance. Hormonal tests for the tion of pituitary adenomas, preferably carried out in an endocrine clinic. Between 60 and 70 % of tumours, in both men and romen, are prolactin-secreting. About 10 to 15 % secrete growth hormone, and a smaller number secrete ACTH. Tumours that secrete gonadotropins and TSH are quite rare. The tumours may be monohormonal or plurihormonal and approximately one-third of pituitary adenomas are composed of nonfunctional (null) cells.

Pituitary tumours usually arise as discrete nodules in the anterior part of the gland (adenohypophysis). The tumours are reddish gray, soft (almost gelatinous), and often partly cystic, with a rim of calcium in some instances. The adenomatous cells are arranged diffusely or in various patterns, with little stroma and few blood vessels; less frequently the architecture is sinusoidal or papillary in type. Variability of nuclear structure, hyperchromatism, cellular pleomorphism, and mitotic figures are interpreted as signs of malignancy, which is exceedingly rare. Tumours less than 1 cm in diameter are referred to as microadenomas and are at first confined to the sella. As the tumour grows, it first compresses the pituitary gland; then, as it extends upward and out of the sella, it compresses the optic chiasm; later, with continual growth, it may extend info the cavernous sinus, third ventricle, temporal lobes, or or fossa. Recognition of an adenoma when it is still confined to the sella is of considerable practical importance, since total removal of the tumour by excision or some form of stereotactic radiosurgery is possible at this stage, with prevention of further damage to normal glandular structure and the optic chiasm.

Amenorrhea-Galactorrhea Syndrome

As a rule, this syndrome becomes manifestative during the childbearing years. The history usually discloses that menarche occurred at the appropriate age; primary amenorrhea is rare. A common history is that the patient took birth control pills and when she stopped, the menstrual cycle did not reestablish itself. On examination, there may be no abnormalities other than galactorrhea. Serum prolactin concentrations are increased (usually in excess of 100 ng/mL). In general, the longer the duration of amenorrhea and the higher the serum prolactin level, the larger the tumour (prolactinoma). The elevated prolactin levels distinguish this disorder from idiopathic galactorrhea, in which the serum prolactin concentration is normal.

Males with prolactin-secreting tumours rarely have galactorrhea and usually present with a larger tumour and complaints such as headache, impotence, and visual abnormalities. With large tumours that compress normal pituitary tissue, thyroid and adrenal function will also be impaired.

Acromegaly

This disorder consists of acral growth and prognathism in combination with visceromegaly, headache, and several endocrine disorders (hypermetabolism, diabetes mellitus). It is due to growth hormone (GH) overproduction occurring after puberty; prior to puberty, GH oversecretion produces gigantism. The diagnosis of this disorder, which is often long delayed, is made on the basis of the characteristic clinical changes, the finding of elevated serum GH values (10ng/mL), and the failure of the serum GH concentration rise in response to the administration of glucose or TRH.

Cushmg Disease

This condition is only about one-fourth as frequent as acromegaly. The clinical effects are the same in all of these disorders and include truncal obesity, hypertension, muscle weakness, amenorrhea, hirsutism, abdominal striae, glycosuria, osteoporosis, and, in some cases, a characteristic psychosis. Seldom is the sella turcica enlarged: visual symptoms or signs due to involvement of the optic chiasm or extension to the cavernous sinus are therefore rare. The diagnosis of Gushing disease is made by demonstrating increased concentration of plasma and urinary cortisol; these levels are not suppressed by the administration of relatively small doses of dexamethasone (0.5 rag four times daily), but they are suppressed by high doses of dexamethasone (8 mg daily). A low level of ACTH in the blood, increased cortisol in the blood, increased free cortisol in the urine, and nonsuppression of adrenal function after the administration of high doses of dexamethasone are evidence of an adrenal source of the Cushing syndrome — usually a tumour, less often a micronodular hyperplasia of the adrenal gland.

Diagnosis of Pituitary Adenoma

This is virtually certain when a chiasmal syndrome is combined with an endocrine syndrome of either hypopituitary or hyperpituitary type. Laboratory data that are confirmatory of an endocrine disorder, as described above, and a ballooned sella turcica in plain films of the skull corroborate the diagnosis. Patients who we suspected of harboring a pituitary adenoma but in whom the Plain films are normal should have high-resolution CT scans with thin-slice techniques in the coronal plane, or preferably MRI. The latter procedure will visualize pituitary adenomas as srnall as 3 mm in diameter and show the relationship of the tumour to the optic chiasm. It also provides the means of the tumour's response to therapy.

Tumours different from pituitary adenomas may sometimes expand the sella. Enlargement may be due to an intrasellar cranopharyngioma$_7$ carotid aneurysm, or cyst of the pituitary gland.

Intraseilar, epithelial-lined cysts are rare lesions. Rarer still are intrasellar cysts that have no epithelial lining and contain thick, dark brown fluid, the product of intermittent haemorrhages. Both types of intraseilar cysts may compress the pituitary gland and mimic the endocrine-suppressive effects of pituitary adenomas.

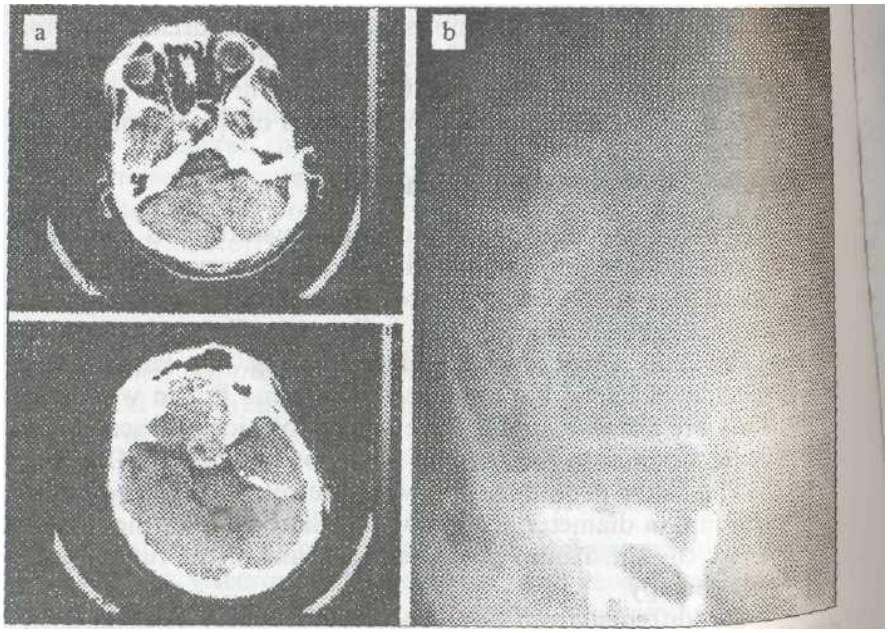


Fig. 46. Adenoma of the hypophysis: a) CT, b) angiography

Glioma of the Brainstem

Astrocytomas of the brainstem are relatively slow-growing tumours that infiltrate tracts and nuclei. They produce a variable clinical picture, depending on their location in the medulla, pons, or midbrain. Most often, this tumour begins in childhood (the peak age of onset is 7 years), and 80 % appear before the twenty-first year. Symptoms have usually been present for 3 to 5 months before coming to medical notice. In most patients the initial manifestation is a palsy of one or more cranial nerves, usually the sixth and seventh on one side, followed by long tract signs hemiparesis, unilateral ataxia, ataxia of gait, paraparesis, and hemisensory and gaze disorders. In the remaining patients the symptoms occur in a reverse order i.e., long tract signs precede the cranial nerve abnormalities. Patients in this group survive longer than those whose illness begins with cranial nerve palsies. The combination of a cranial nerve palsy or palsies on one side and motor and/or sensory tract signs on the other always indicates brainstem disease.

The main problem in diagnosis is to differentiate this disease form of multiple sclerosis, a vascular malformation M pons (usually a cavernous hemangioma), and brainstem encephalitis, and to distinguish the focal from the diffuse type of glioma of most helpful procedure in diagnosis and prognosis is MRI.

The treatment is radiation, and if increased intracranial D sure develops, ventricular shunting of CSF becomes necessa Adjuvant chemotherapy has not been helpful. These tumours contrast to the diffuse type, usually respond well to partial res'ew tion and permit long-term survival because they recur only slowly and do not undergo malignant transformation. The rare cystic glioma of the brainstem, a pilocytic tumour like its counterpart in the cerebellum, is treated by resection of the mural nodule.

Glioma of the Optic Nerves and Chiasm

This tumour, like the brainstem glioma, occurs most frequently during childhood and adolescence. In 85 % of cases, it appears before the age of 15 years (average 3.5) and twice as frequent in girls than in boys. The initial symptoms are dimness of vision with constricted fields, followed by bilateral field defects of homonymous, heteronymous, and sometimes bitemporal type, progressing to blindness and optic atrophy with or without papilledema. Ocular proptosis from the orbital mass is the other main symptom. Hypothalamic signs (adiposity, polyuria, somnolence, and genital atrophy) occur occasionally. Scanning by MRI, CT, and ultrasound will usually reveal the tumour, and

radiographs will show an enlargement of the optic foramen (greater than 7.0 mm). This finding and the lack of ballooning of the sella or of suprasellar calcification will exclude pituitary adenoma, Hand — Schuller — Christian disease, sarcoidosis, and craniopharyngioma. In adolescents and young adults, the medial sphenoid, olfactory groove, and intraorbital meningiomas (optic nerve sheath meningioma) are other tumours that cause blindness and proptosis. If the entire tumou is prechiasmatic (the less common configuration), surgical extirpation can be curative. For tumours that have infiltrated the chiasm or are causing regional symptoms and hydrocephalus, partial **excision** followed by radiation is all that can be offered. Both g'[10]" mas and nontumourous gliotic (hamartomatous) lesions of the op tic nerves may occur in von Recklinghausen's disease; the la* are sometimes impossible to distinguish from optic nerve gliomas-