

CHAPTER 27

Cerebral Hemispheres: Neuropathology and Clinical Correlation II. Non-Vascular Syndromes

PART I: TRAUMA

In the era of the automobile, bicycle, and motorcycle, trauma to the head constitutes one of the most frequent neurological problems presented to emergency room physicians. Not all head injuries involve the brain. Significant scalp lacerations and simple skull fractures may be present without the development of significant neurological deficits. On the other hand, closed head injuries may be present with significant neurological signs but without major external signs of head trauma (i.e., scalp and skull appear intact).

Concussion: Perhaps the most common neurological syndrome occurring in relation to head trauma is the cerebral concussion, a syndrome characterized by a transient alteration of consciousness and of higher cerebral functions lasting a matter of minutes to hours, following a blow to the head. Consciousness may or may not be transiently lost at the onset. The patient complains of "being in a dazed state" with blurring of vision and a sense of unsteadiness. Memory is often impaired for events during this period following the injury: post-traumatic amnesia. The transient inability to record and recall events that occur after the traumatic event is called anterograde amnesia. In addition, memory for events which occurred minutes, hours, or even several days prior to that injury may be impaired: retrograde amnesia. As recovery occurs, this period of retrograde amnesia may shrink.

No definite pathology has been associated with cerebral concussion; the pathophysiology remains unclear. There is some indication that differential acceleration or deceleration of the brain and skull may force the cerebral cortex against the hard surface of the skull producing a transient neuronal dysfunction. Rotational forces may also set up stresses that result in the stretching (shearing) of white mat-

ter systems at a subcortical and brain stem level.

Contusions and Lacerations (Fig 27-1): More serious injuries of the cerebral hemisphere involve contusions, lacerations, intracerebral hemorrhages and edema.

Contusions (local areas of swelling and capillary hemorrhage resembling bruises) are found particularly at the anterior temporal poles and the under surfaces of the frontal and temporal lobes. These contusions of the cerebral cortex occur as a result of the sudden impact of the cortex against the bony wall of the skull. The anterior portions of the anterior and middle fossa provide relatively constricting compartments favoring the development of such contusions. Contusions may directly underlie the site of the blow to the skull (so-called coup injuries) or may be across from the site of injury (so-called contra coup injuries). When examined at autopsy years later, the brain may show small orange-yellow colored areas of depression on the orbital-frontal and anterior-temporal areas (plaques jaunes).

Intracerebral hemorrhages may also be present. These are usually multiple and small.

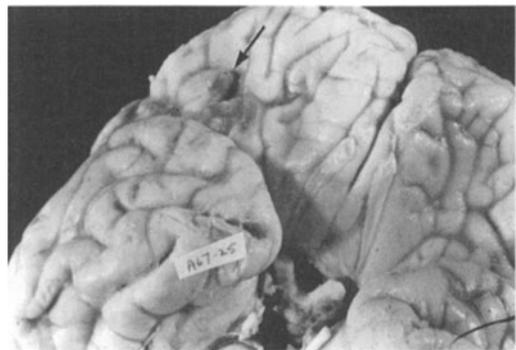


Figure 27-1. Old contusion and laceration of the right orbital frontal area (arrow). This 59-year-old white male had a long history of heavy alcohol intake. In addition to the traumatic lesion shown above, the patient had clinical and pathological evidence of an old Wernicke's encephalopathy involving the mammillary bodies and of alcoholic cerebellar cortical degeneration. (Courtesy of Dr. Jose Segarra)

Occasionally, a single large hematoma may be present requiring surgical therapy if mass effects are present.

Lacerations of the brain involve actual tears in the cortical surface. Both lacerations and contusions may result in the appearance of some red blood cells in the subarachnoid space. In general, patients with contusion and laceration have a loss of consciousness in relation to the injury. Residual alterations in mental function, memory and personality are often noted. Such alterations are uncommon with a simple concussion. Focal neurological findings may be present during the acute stage, at times remaining as residual deficits. Severe focal deficits such as hemiparesis or aphasia are, however, usually absent.

Complications of Skull Fractures: Certain types of skull injuries provide serious problems as regards the brain and require surgical attention. Thus, depressed skull fracture may compress the cerebral cortex, with bony splinters lacerating the dura and cortex.

Penetrating head injuries (the object causing trauma has penetrated the skin, bone and meninges) may introduce contaminated material into the brain, producing abscess formation and meningitis. Fractures involving the cribriform plate with laceration of the overlying dura and arachnoid may result in the loss of olfactory sensation (anosmia) and cerebrospinal rhinorrhea: the drainage of spinal fluid through the nose. The presence of such a pathway, of course, allows for the ready entry of bacteria from the nasopharynx into the cerebrospinal fluid spaces, producing recurrent episodes of meningitis. Air may also enter the intracranial cavity through this passageway. Both air and infection may also enter when skull fractures extend into any of the paranasal sinuses or the middle ear. In the latter instance, a cerebrospinal fluid otorrhea may occur: drainage of spinal fluid from the external ear canal. Such basilar skull fractures may extend across the petrous pyramid or tear the tympanic membrane. Blood may be present in the external ear canal or behind the tympanic membrane. If the basilar skull fracture extends into the sigmoid

sinus, the tissue over the mastoid may show delayed hematoma with discoloration of the skin and subcutaneous tissue - ("Battle sign").

EXTRADURAL HEMATOMAS AND SUBDURAL HEMATOMAS

Of great importance from the neurological standpoint are these two traumatic conditions in which progressive compression of the cerebral hemispheres occurs. These are conditions where early recognition and treatment will produce excellent results. The failure of recognition will result in progressive deterioration of neurological status with death as the eventual outcome. Note that large traumatic intracerebral hematomas will also produce a progressive course and these lesions may also benefit from surgical therapy (see also Zervas and Hedley-White 1972). The use of CT scan has revolutionized the diagnostic approach to these problems: (see Cordobes et al 1981, Markwalder 1981, Masters et al 1987).

Extradural Hematoma: Extradural hematoma is a complication of skull fractures that extend across a groove containing a meningeal artery usually the middle meningeal artery. Less often the skull fracture has torn a large venous sinus. Since the bleeding is usually arterial and brisk and the extradural space is narrow (normally the dura is closely applied to the skull), compression of the cerebral hemisphere soon results with the rapid development and progression of neurologic symptoms. The classic description is usually that of a short period of unconsciousness related to the acute trauma, then a short lucid interval, which is followed by progressive confusion and coma. A rapidly progressive hemiparesis is often noted with the development of a fixed dilated pupil on the side of the hematoma indicating uncal herniation by the mass that may be placed laterally over the temporal lobe. At other times, as in the following case history, these lateralized findings may be overshadowed by the rapid progression to a stage of functional midbrain transection.

Case 27-1: This twenty-two-year-old, white airman, during a winter storm, was

involved in an auto accident at 11:30 p.m., in which he struck his head against the windshield. The patient apparently was dazed, perhaps unconscious, for a matter of seconds to minutes. He was taken by ambulance to the emergency room of the nearby army hospital where a brief evaluation indicated that the patient was alert, without definite neurological findings, but skull X-rays did indicate a linear fracture over the right temporal area

The patient was apparently alert upon his arrival on the ward. However, by 5 a.m., the patient was reported by the nurses to be agitated and confused.

Neurological examination: (8 a.m.)

Mental Status: The patient was agitated and unable to cooperate. He was moving all limbs sitting up in bed, holding his head, which was tender to palpation moaning and hyperventilating to a marked degree. He answered only occasional questions and then with a yes or no. **Cranial Nerves:** Pupillary responses were sluggish. The right pupil was perhaps slightly larger and slightly more sluggish than the left. **Reflexes:** Deep tendon reflexes were increased bilaterally. Plantar responses were bilaterally equivocal.

Neurological diagnosis: Possible evolving acute bilateral epidural or subdural hematoma

Subsequent course: Progression occurred. By 4 pm, the patient was now deeply comatose with little response to stimulation. The pupils were now bilaterally fixed and dilated. The four limbs were extended in a decerebrate posture with significant spasticity on passive motion. The degree of spasticity in the upper limbs could be modified by tonic neck maneuvers. The plantar responses were bilaterally extensor. Spontaneous respirations were now irregular and infrequent, and the patient required the assistance of a mechanical respirator.

Revised Neurological diagnosis: Acute tentorial herniation with brain stem compression secondary to epidural hematoma.

Subsequent course: A general surgeon immediately placed burr holes and evacuated an epidural hematoma over the right temporal-parietal area. He coagulated and ligated a

bleeding middle meningeal artery branch. There was a rapid improvement in the patient's status. The patient returned to active duty but was experiencing some problems related to changes in recent memory, motivation and personality.

Subdural Hematomas: Subdural hematomas (*Fig. 27-2, 27-3*) represent the accumulation of blood within the subdural space overlying the cerebral convexities. Such hematomas may be acute, subacute or chronic. The acute and subacute types are clearly associated with trauma. The acute type is usually associated with other significant injuries of the brain such as cerebral contusion, laceration and intracerebral hematomas. With tears in the arachnoid, blood from the lacerations passes into the subdural space. Moreover, small bridging veins from the pia arachnoid to the superior sagittal sinus are also likely to be torn. The clinical picture of the acute subdural hematoma is often then modified by the clinical manifestations of these associated injuries. At times, however, the typical picture of a rapidly progressive supratentorial space-occupying lesion with progressive obtundation of consciousness and the signs of tentorial herniation will develop in acute (24 to 48 hours) relationship to the head injury. The chronic variety may appear after closed-head trauma, often apparently trivial. At times, there may be no definite history of trauma.

The subacute and chronic subdural hematomas develop after a variable latent period of days, weeks, or months following the injury. The bleeding is venous from small bridging veins passing from the pia arachnoid to the superior sagittal sinus. The resultant accumulation of blood then is relatively slow. Associated injuries to the brain are usually not present. The blood in the subdural space is not readily removed and remains adherent to the dura. Fibroblasts and blood vessels grow from the dura at the edges of the clot, producing a thin membrane that separates the clot from the arachnoid. At the same time, a thicker layer of connective tissue and blood vessels is forming a membrane where the clot is adherent to the

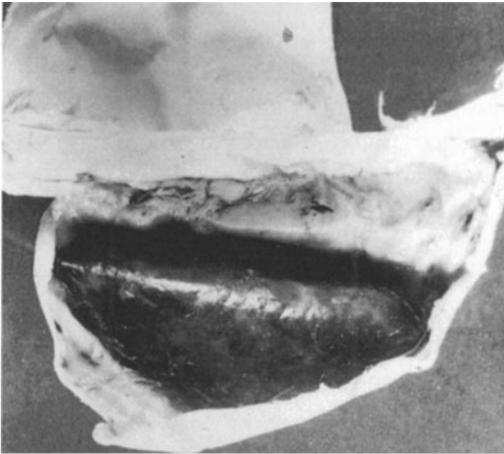


Figure 27-2. Subdural hematoma. This 69-year-old patient with Parkinson's disease had many dizzy spells and had fallen frequently. (Courtesy of Drs. John Hills and Dr. Jose Segarra)

inner layer of the dura. The hematoma often continues to increase in size apparently for several reasons: continued venous oozing may occur; moreover, bleeding may occur from the blood vessels that are growing into the hematoma from the dural surface. Finally, it has been suggested that as some breakdown occurs within the clot, a fluid with high protein content is produced. The resultant fluid of high osmotic pressure then attracts more fluid into the hematoma.

The clinical manifestations are those of a progressive supratentorial mass lesion. At times, progressive focal symptoms and signs are present; for example, hemiparesis, aphasia and focal seizures. Eventually, alterations in consciousness occur, often of a fluctuating nature. With eventual tentorial herniation, a fixed dilated pupil and the signs of a progressive functional midbrain transection are noted. Often, however, a syndrome is present in which focal symptoms and signs are not prominent, perhaps reflecting the fact that bilateral subdural hematomas are present in a high percentage of cases. The resultant picture then is that of a progressive state of confusion with fluctuating alterations in consciousness. A bilateral grasp reflex is often present. Eventually, if untreated, coma and the signs of tentorial herniation develop. In both types of

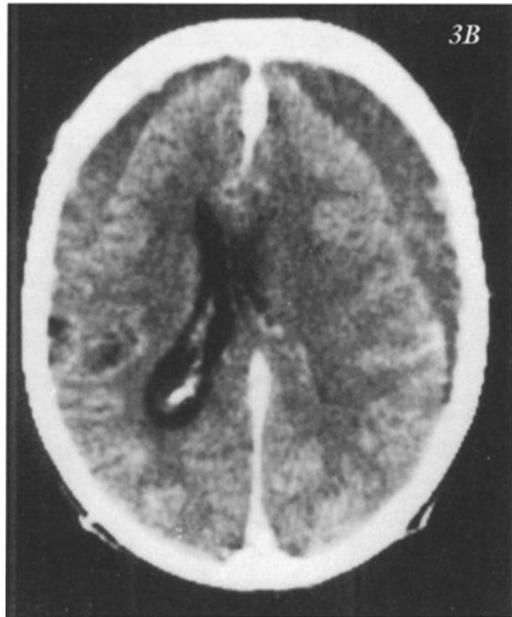
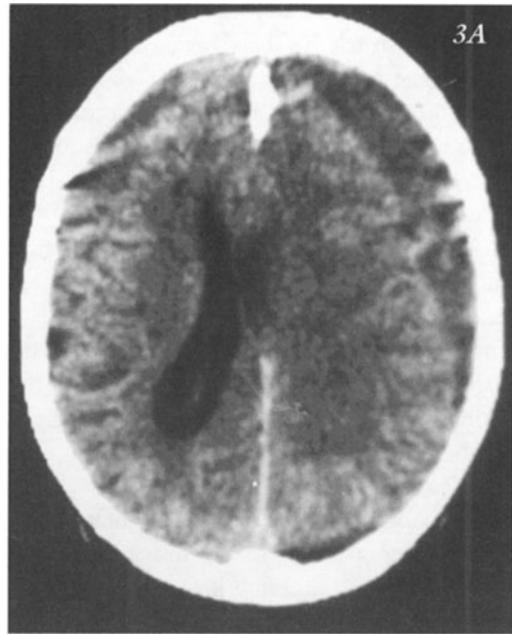


Figure 27-3. Chronic subdural hematoma, bilateral CT Scans. Case History 27-2. A) Non-contrast enhanced. B) Contrast Enhanced: note enhancement at membrane margins. This 83-year-old female - 3 months after a motor vehicle accident in which she struck her head, developed fluctuating confusion and lethargy. (See text for details).

syndrome, progressive headache may be present although this complaint as well as the past history of head trauma may be difficult to elicit when the patient is admitted to a hospital in

a confused state.

Case 27-2. (Patient of Dr. Alex Danylevich). This 83-year-old white female struck her head in a motor vehicle accident 2 months prior to admission. She had sustained fractures of her ribs and left clavicle. She had a scalp hematoma in the right frontal area. She was admitted to her local hospital at that time for several days. She was described as having post-traumatic antero-grade and retrograde amnesia and obtundation, which cleared over her several day hospital stay. She returned to her usual activities but then was readmitted with a three-day history of increasing confusion, lethargy followed by a mute state.

Neurological examination: *Mental status:* The patient was lethargic, mute and did not follow commands even when relatively alert. *Cranial nerves:* Pupils were 2 mm. and reactive. There were sudden paroxysmal nystagmoid deviations of the eyes to the right. *Motor system:* Tone was increased in the right leg. *Reflexes:* Plantar responses were extensor bilaterally.

Clinical diagnosis: Chronic subdural hematomas, probably bilateral.

Laboratory data: The *CT scan (Fig. 27-3)* demonstrated significant bilateral chronic subdural collections much denser on the left where the lateral ventricle was obscured and shifted to the right. *Serum sodium* was low at 117 mEq/liter

Hospital course: Serum sodium was corrected. Then, bilateral subdural hematomas were removed via burr holes on the right and a bone flap on the left where substantial chronic membrane and fluid were found. Neurological examination eight hours after conclusion of the procedure, indicated an alert patient who had no apparent language disorder and no weakness. She did develop transient right face and hand focal motor seizures that were treated with anti-convulsants.

There are patients who are at increased risk for subdural hematomas: patients receiving anticoagulant medications, or with bleeding disorders, (e.g., as in leukemia. The elderly, chronic alcoholics, and patients with

Parkinson's disease are also at increased risk perhaps because such population groups are more prone to unsteadiness and falls (See discussion of chapter 18). In the patient with cortical atrophy as in Alzheimer's disease, the bridging veins may be stretched and thus more prone to tear. Because of the atrophy, a large amount of blood may accumulate in the subdural space without producing early symptoms of headache and other symptoms.

The problem also exists in the infant during the first year of life. The picture presented, however, differs significantly from that seen in the adult because in the infant, separation of the sutures may occur, allowing the intracranial cavity to expand. The onset is then often non-specific and nonfocal: an enlargement of the head, a failure to thrive, a failure to gain weight, and a failure to reach developmental landmarks. At times, generalized seizures, vomiting, and papilledema may be noted. The etiology often relates to presumed birth trauma.

A related problem is the occurrence of subdural effusions in infants following H.influenza meningitis.

MANAGEMENT OF SEVERE HEAD TRAUMA

Severe head injuries represent major problems requiring intensive care. Such patients generally are brought to the emergency room in coma or an obtunded state. As opposed to the patient with a simple concussion (where any loss of consciousness is brief - minutes), these patients continue with an altered level of consciousness for hours, days, weeks or months. From a pathological standpoint, these patients are found to have contusions, laceration, and multiple hemorrhages within the substance of brain and associated edema and infarction. These findings may be diffuse or concentrated in the diencephalic and midbrain areas involved in maintaining consciousness. At times, the direct effects of trauma have been complicated by cardiopulmonary arrest due to chest injuries or on a central basis producing anoxic encephalopathy. Most do not have

epidural or subdural hematomas (epidural in 15%, subdural in 15%). The details of management are considered in Jennett and Teasdale 1981, Bullock and Teasdale 1990, Jaffe and Wesson 1991, White and Likavec 1992, and Ropper, et al 1988. Essentially, the emergency critical care management of the traumatic comatose patient involves the following major steps.

1. ABC -Stabilization of vital functions including Airway, Breathing and Circulation (control of bleeding and blood pressure).

2. Rapid neurological evaluation with rapid rating of the level of consciousness (see chapter 29).

3. Emergency CT scan should be obtained. A simple cervical spine series at the same time should serve to rule out cervical fractures and dislocations.

4. Epidural hematomas, significant subdural hematomas and large focal intracerebral hematomas require emergency neurosurgical intervention.

5. Monitoring and management of increased intracranial pressure are necessary where contusions, edema, small intracerebral hematomas, and small ventricles are present on CT scan).

6. Temperature, electrolytes and fluid balance and nutrition must be maintained to avoid the metabolic causes of coma.

7. Seizures must be treated.

8. Prevention of deep vein thrombosis in the lower extremities, and of the subsequent complication of pulmonary embolus (Geerts et al, 1994).

Late Effects Of Head Trauma 1) *Post-Traumatic Epilepsy*: The seizures may be focal or generalized. Penetrating injuries of the head, as in wartime wounds from bullets or shrapnel, are likely to be associated with post-traumatic seizures. In the World War II series of Watson, 41.6 percent of such patients developed seizures within 3 years of the injury, the majority within 6 to 12 months. There is some evidence that factors such as the location of the wound within the cerebral hemisphere and the complication of abscess may influence the inci-

dence of such post-traumatic seizures. Most head injuries in civilian life, however, are not penetrating missile wounds but rather blunt and non-penetrating injuries (closed head trauma), and under these circumstances, seizures are much less common. Thus, in the series of Jennett, the overall incidence of seizures in 1000 consecutive blunt head injuries was approximately 5 percent over a four-year period. In summary, the post-traumatic seizures are more likely to occur in those head injuries where actual structural damage of the cerebral cortex has occurred.

2) *Post-Concussion Syndrome*: Another relatively common late complication of head trauma is the post-traumatic or postconcussion syndrome consisting of recurrent episodes of headache and dizziness (vertigo or light-headedness). The episodes often appear to be precipitated by exercise or change in posture from the recumbent to the upright. The severity and duration of the syndrome bears no relationship to the severity of the trauma; the episodes may continue for years after a trivial injury. In a few cases, the vertigo may be related to a traumatic disturbance of the labyrinth. Patients may develop benign positional vertigo. In many cases, the dizziness is actually a light-headedness related to anxiety and hyperventilation. In general, no actual pathology is found. As a general rule, stable, well-motivated individuals who are anxious to return to their previous occupation or studies do not experience this syndrome in severe degree. On the other hand, individuals with disorders of personality or psychoneurosis or with problems in adjusting to studies or employment, appear to be severely affected (Evans 1992).

In recent years, there has been recognition of possible long duration changes in memory and cognitive function following concussion or other mild head trauma primarily on the basis of neuropsychological testing (see Capruso and Levin 1992, Packard 1994 for additional discussion of cognitive effects of head trauma).

PREVENTION

Trauma is the most frequent cause of death

and disability in children and young adults. Neurological trauma to brain and spinal cord, constitutes the major reason for prolonged costly hospitalizations in young adults since such patients require prolonged intensive critical unit and low term rehabilitative care. The long-term effects of interruption of what were once hopeful productive careers cannot be calculated simply in terms of the billions of dollars involved but must also take into account the personal and family miseries, which are incurred. Many of the problems are preventable. Table 27-1 summarizes the measures available for prevention of head injuries.

Other traumatic problems include a.) anosmia as in case 30-3 on CDROM (shearing of the olfactory filaments passing through cribriform plate), b.) carotid/cavernous fistula and c.) dissections of the carotid and vertebral arteries.

PART II: NEOPLASMS

Based on the previous chapters, it is evident

TABLE 27-1: PREVENTION OF HEAD INJURIES

PREVENTATIVE MEASURES	RESULTS OF PREVENTATIVE MEASURE
1. Tri-corner seat belts	Mandatory use has been demonstrated to significantly reduce head, face, chest and spinal cord injuries.
2. Strict enforcement of driving regulations regarding alcohol and drugs	The majority of severe accidents involve the disregard of these regulations. Often the use of these agents is combined with excessive speed.
3. Mandatory use of safety helmets by bicycle and motorcycle riders	Reduces the frequency of: a. Head and neck injury deaths, b. Severe head trauma morbidity c. Minor head and neck injuries, d. Post-traumatic epilepsy - one of the few preventable causes of one of the major diseases of the nervous system.
4. Strict regulation of boxing – professional and amateur with mandatory use of helmets. Compulsory suspensions or revocations after knockouts should be required Based on long-term neurological, EEG and CT scan studies of professional boxers (Ross et al 1983). Many medical organizations including the AMA and the American Academy of Neurology have gone so far as to call for the elimination of all professional boxing	Reduce the incidence of multiple small contusions and lacerations of the orbital frontal and temporal areas etc, which result in a chronic frontal lobe syndrome, "the pinch drunk" state and possible post traumatic Parkinsonian state.
5. Effective regulation of sales of arms.	Weapons constitute a major cause of injuries and deaths in adolescents and young adults.

that particular tumors occur at particular ages. In childhood most intracranial tumors are infratentorial; in adult life, the larger proportion are supratentorial. Meningiomas, glioblastomas, metastatic carcinomas, pituitary adenomas, vestibular Schwannomas (or neurinomas), are tumors of the adult. On the other hand, medulloblastomas and ependymomas are primarily tumors of childhood, while brain stem and spinal cord gliomas are found primarily in older children, adolescents and adults

It is also evident that knowledge of the cell type of a tumor taken in isolation does not necessarily enable the observer to predict the future biological and clinical behavior of the tumor. Identity of the cell type and knowledge of the location of the tumor does allow for a higher order of prediction.

Thus, glial tumors may arise in the cerebral hemisphere, the brain stem, and the cerebellum. The biological behavior of the tumor in each location is quite different. Thus, most glial tumors of the cerebral hemispheres in the adult are highly malignant. They are rapidly

growing invasive necrotic tumors with variable cell morphology and frequent nuclear mitotic figures. The brain stem and spinal cord astrocytoma, usually seen in children and young adults, on the other hand, is usually slower growing and has a more constant cellular and nuclear pattern. The cerebellar astrocytoma is a limited cystic and encapsulated tumor of low histological grade, which can be removed in its entirety with essential cure of the patient.

The clinical manifestations of a particular tumor are determined in part by the cell type of the tumor (astrocytoma, meningioma) and its biological activity (benign meningioma, low-grade astrocytoma, or highly malignant astrocytoma). Much more important in the determination of clinical signs and symptoms is the location of the tumor. This applies to both the local symptoms and signs (focal cortical symptoms and signs or posterior fossa symptoms and signs) and to the general symptoms and signs such as headache, vomiting, drowsiness and papilledema that reflect the increased intracranial pressure resulting from the tumor mass, cerebral edema, and blockage of the ventricular system. Focal seizures are more likely to occur with low-grade gliomas and meningiomas and less likely to occur with highly malignant gliomas.

Headaches: Headache in patients with brain tumors may reflect not only increased intracranial pressure but also the direct or indirect compression of pain sensitive intracranial structures such as blood vessels, dural sinuses, meninges or cranial nerves at the base of the brain. At the present time, less than 50% of patients with brain tumors complain of headaches. Headache as an early symptom is more frequent in patients with highly malignant gliomas, and less frequent in low-grade gliomas and meningiomas. Supratentorial tumors tend to produce frontal, temporal, orbital or parietal located headaches. Infratentorial tumors tend to produce occipital or upper cervical located headaches.

In general, patients with headaches alone have another (non tumor) explanation for the headaches. This includes tension headaches,

migraine headaches, or disease of the nose, nasal sinuses, orbits or acute or chronic disease of the cervical spine. Headaches that awaken the patient from sleep, or are produced by positional changes or by coughing or similar maneuvers should raise questions about a possible non-benign pathology. Even under these circumstances, the majority of patients will fall into a benign pathology group. Acute onset of headache, "the worst ever" may indicate a subarachnoid hemorrhage or meningitis.

1. *Migraine Headaches.* In general migraine (vascular headaches) occur intermittently, are throbbing, accompanied by nausea and vomiting and may be unilateral or bilateral. They are classified as migraine with aura if focal symptoms such as visual phenomena lateralized tingling or other cortical phenomena precede the headache. They are classified as migraine without aura if the headache occurs without these phenomena.

2. *Periodic cluster headache.* This variety of unilateral vascular headache often awakens the patient from sleep each night over a period of 1 to 2 weeks. They are throbbing but also involve acute sharp pain localized to the eye. Usually, the headache is accompanied by unilateral tearing of the involved eye and unilateral nasal congestion. They are usually relieved by inhalations of oxygen. Such headaches must be differentiated from the unilateral pain of glaucoma. Acute maxillary sinusitis may also produce unilateral pain in the maxillary and ophthalmic distribution accompanied by nasal congestion, local tenderness, swelling and erythema.

3. *Muscle tension headaches* tend to occur on a daily basis, and tend to occur as the problems of the day build up. They are described as a pressure or aching type pain located in the frontal areas but often spreading to the temporal and occipital areas. Often increased tension may be palpated in the temporalis, frontalis or cervical muscles. Degenerative disease of the cervical spine is frequent and such patients may have chronic muscle tension and aching pain in the cervical and occipital areas.

4. Another common cause of headache is

occipital neuralgia. This occurs in patients with prior whiplash injuries who have unilateral sharp pains in the distribution of the occipital nerves or the cervical 2-nerve root. These patients will have significant local tenderness on palpation of the occipital nerve at the occipital notch. The pain is relieved by cervical traction or local injection of the occipital nerve.

Brain Tumor Epidemiology: The overall relative frequency of the various types of tumors affecting the central nervous system varies from series to series depending on whether a surgical or autopsy series is being reported. In addition, the particular interests of the neurosurgeon have often resulted in a specialized tumor type being referred to a particular neurosurgeon. Table 27-2 presents the data

TABLE 27-2 RELATIVE FREQUENCY OF VERIFIED INTRACRANIAL TUMORS (AFTER MERRITT, 1967)

TYPE OF TUMOR	COMBINED NEUROSURGICAL SERIES OF 4349 CASES (Grant and Cushing)	AUTOPSY SERIES OF 3010 CASES (Courville)
Type of Tumor	Percent of Total	Percent of Total
Gliomas	43.0	41.5
Meningiomas	15.0	11.6
Metastatic Tumors	6.5	23.7
Pituitary Adenomas	13.0	3.4
Acoustic Neuromas	6.5	2.5
Congenital Tumors	4.0	3.5
Blood Vessel Tumors*	3.0	7.8
Miscellaneous: papillomas, Granulomas** and sarcomas	9.0	5.7

* There are very few true tumors of blood vessels (hemangioblastomas and angioblastic meningiomas). Today many of the "tumors" of this group would be considered malformations.

** Today Infectious granulomas would not be considered in this series. In some parts of the world tuberculomas and parasitic granulomas still constitute a significant percentage of mass lesions coming to surgery or autopsy.

of two neurosurgeons with extensive experience in the surgery of brain tumors. The autopsy data of an earlier period when the postmortem examination was more frequently performed is also presented.

Metastatic tumors are under-represented in the operative series since patients with multiple metastatic tumors are not considered surgical candidates. Pituitary adenomas were of particular interest to Cushing and, thus, are over-represented in the operative series. The true clinical frequencies are somewhere between the operative and autopsy incidences. It is important to realize that silent meningiomas may be found on CT scans or MRI scans or at autopsy in older patients. Small pituitary adenomas are found frequently at autopsy.

It is also important to place in perspective, the overall frequency of brain tumors.

1. Primary intracranial tumors diagnosed prior to death occur in 11.8 patients per 100,000 per year (Radhakrishman et al, 1995).

2. Asymptomatic tumors. In the same series 7.3 patients per 100,000 per year are found to have asymptomatic tumors.

3. Pediatric age group: Brain tumors are the most frequent form of all solid neoplasm (medulloblastomas, brain stem and cerebellar astrocytomas, ependymomas). Among all malignancies in the pediatric age group, brain tumors are out ranked only by leukemia. In the age group 15-34 years, malignant gliomas are the third leading cause of death from cancer.

4. Overall malignant gliomas alone account for 2.5% of deaths due to cancer. Among adults, more die of primary brain tumors than of Hodgkin's disease or of multiple sclerosis.

5. Moreover, 13% of the overall 385,000 cancer deaths per year have some clinical evidence of central nervous system involvement. Autopsy studies suggest that 25% of patients dying of cancer have intracranial metastases. With cancer of the lung, the percentage is even higher.

Etiology Of Primary Brain Tumors

For the majority of cases, no specific factors can be identified.

1. Radiation of the head early in life for unrelated reasons, certainly does significantly increase the risks, for all types of tumors involving the nervous system including, gliomas (2.6X), meningiomas (9.5X), and nerve sheath tumors (18.8X), compared to a matched control group. Overall risk for 1.5Gy neural tissue dose was 6.9X control and 20X control for 2.5Gy tissue dosage. (Ron et al 1988).

2. A possible increased risk for the development of gliomas following occupational exposures in the petrochemical, chemical and rubber industries has been discussed by a number of authors (Selikoff and Hammond 1982).

3. Head injury of a significant nature, e.g., depressed skull fractures, may be associated with meningiomas.

4. In a small number of patients, certain familial syndromes may be present as predisposing factors, e.g., *neurofibromatosis* associated with acoustic neuromas, meningiomas and gliomas (of various types - including optic nerve), and *tuberous sclerosis* associated with astrocytomas.

5. Black (1991) and Shapiro and Shapiro 1992 have reviewed concepts of oncogenesis, as applied to primary brain tumors, Oncogenes that potentiate or initiate cell mitosis may behave inappropriately or excessively in neoplastic cells. Alternatively, or in addition, neoplastic cells may have lost tumor suppressor sequences. Chromosomal analysis has identified deletion loci on chromosome 22 in meningiomas, chromosome 17 and 22 in acoustic neuromas and chromosomes 10 and 17 in astrocytomas. Chromosome 7 has been implicated with increased frequency in the cells of malignant gliomas.

5. Other Factors. The role of various other growth factors and of immune mechanisms remains to be clarified. Hormonal factors are undoubtedly of importance in meningiomas. These tumors are more common in women than men (2:1 ratio), may undergo growth during pregnancy and are more common in women with carcinoma of the breast. Estrogen and progesterone receptors have been demonstrated in meningiomas (Lesch et al 1987).

PRIMARY INTRINSIC TUMORS OF NEUROEPITHELIAL ORIGIN

The most frequent tumors affecting the cerebral hemispheres are those arising from glia. Those of the astrocytic series are by far the most frequent whether operative or autopsy series are considered (Table 27-3). Within this group the glioblastoma is the most frequently encountered, based on autopsy statistics. In the era of Cushing, glioblastomas were often not subjected to surgery. (See below for more recent data and approaches). Oligodendrogliomas are relatively infrequent and ependymomas involving the cerebral hemispheres are rare.

Astrocytic tumors. In general these tumors infiltrate the cerebral hemisphere. The astrocytomas have been subdivided into various types. According to the classification of Kernohan and his associates (1952), these tumors were subdivided into four grades based on their histological degree of malignancy. This classification to a variable degree, replaced the older nomenclature of Bailey and Cushing (1926), which classified the glial tumors on an embryological basis (The tumor was classified after the actual or hypothetical embryological cell of closest resemblance). More recent classifications have utilized features, which correlate with prognosis (see Burger et al 1985, 1987; Daumais-Duport et al 1988). Features of importance in grading are degree of (1) hypercellularity; (2) pleomorphism, including nuclear atypia and mitosis; (3) vascular proliferation; (4) necrosis.

In the discussion, which follows, we will utilize the several classifications as well as the most recent classification of the World Health Organization as modified by DeAngelis (2001)

From a prognostic standpoint, the following grades of astrocytoma are recognized.

A. The low grade Astrocytoma Tumor (grade I or II astrocytoma). This is a mildly hypercellular tumor with a variable degree of pleomorphism but with no vascular proliferation and no necrosis. There are increased number of mature astrocytes of relatively normal appearance with no evidence of mitosis. Those

arising in the cortex are composed predominantly of protoplasmic astrocytes and were referred to as “gemistocytic”; the cell resembles reactive astrocytes. Those arising in the white matter are composed predominantly of fibrillary astrocytes and sometimes referred to as “piloid or pilocytic”. Grossly, the lesion is non-encapsulated, firm, and granular and gray. Cysts may be present. At times, the only hint of the lesion may be a lack of distinction between gray and white matter. On CT the cyst may be evident. The lesion, however, is usually best seen on MRI scan, which initially does not demonstrate tumor enhancement.

Grade I - Mild, hypercellularity with little pleomorphism or mitosis. The major example is the pilocytic astrocytoma that is predominantly a tumor of children and adolescents. The predominant cell type is usually the fibrillary astrocyte, a relatively uniform elongated mature astrocyte infiltrating along white matter tracts and often found in the pons, optic chi-

asm and diencephalon. The term polar spongioblast was at one time applied to this type of tumor.

Grade II - The major example in this group is the low grade fibrillary astrocytoma demonstrating a greater hypercellularity with greater pleomorphism (mitosis present) but with no vascular proliferation or necrosis. Most (65-95%) present with seizures either focal or secondarily generalized and initially the neurological examination may be without focal features. Most eventually progress to high-grade malignant gliomas. The appearance of progressive neurological findings and of tumor enhancement in the MRI or CT scan may signify such a progression. The median survival despite therapy is 5 years but some survive for 10-15 years. Case 27-3 presented on CD ROM provides an example of the course of such a tumor with onset of generalized seizures at age 30 and followed for over 11 years prior to surgery and radiotherapy.

B. Malignant Astrocytoma: These tumors

TABLE 27-3 THE OVERALL INCIDENCE OF VARIOUS TYPES OF ALL VERIFIED NEUROEPITHELIAL TUMORS*

TYPE OF GLIOMA	NEUROSURGICAL SERIES (CUSHING) Total Number= 862 PERCENT	AUTOPSY SERIES (COURVILLE) Total Number= 1259 PERCENT	AVERAGE SURVIVAL: MONTHS AFTER ONSET OF SYMPTOMS**
Astrocytoma grade I	30.0	23.0	76
Astrocytoma grade II	4.0	1.0	28
Glioblastoma (Astrocytoma grades III & IV)	24.0	52.0	12
Polar Spongioblastoma	4.0	2.0	46
Ganglioglioma	0.3	2.0	-
Oligodendroglioma	3.0	1.0	66
Ependymoma	3.0	6.5	32
Medulloblastoma	10.0	6.0	17
Pinealoma	2.0	1.0	-
Unclassified	20.0	4.0	-

* The series are not restricted to the cerebral hemisphere but include all gliomas.

** After Merritt 1967

correspond to histologic grades III and IV and unfortunately are the most common glial tumors with an annual incidence of 3 to 4 per 100,000 populations. Two tumors are included: the anaplastic astrocytoma and the very malignant glioblastoma. Both types of tumor have a significant contrast enhancement on CT and MRI scans which is often an irregular ring like area at the apparent margin. In actuality the tumor extends beyond this border into the adjacent tissue.

Grade III: The anaplastic astrocytoma tends to begin between the ages of 30 to 50 years. Characteristics include a significant degree of hypercellularity, a significant degree of pleomorphism and a moderate degree of vascular proliferation (*Fig 27-4*). Median survival with aggressive treatment is approximately three years. Treatment is similar to that discussed for glioblastoma below.

Grade IV: The glioblastoma multiforme accounts for 80% of all malignant gliomas, with the highest frequency of onset of symptoms between the ages of 50 to 70 years. However there are two categories within this group: primary glioblastomas that tend to begin in older individuals (mean age 55 years) and secondary glioblastomas, occurring in somewhat younger individuals (mean age 45 years). These latter tumors have begun as a lower grade of tumor and then have secondarily evolved so that younger patients often appear to have a longer duration of disease. From the histological

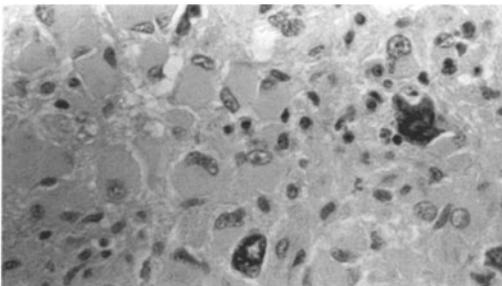


Figure 27-4. Gemistocytic astrocytoma, demonstrating a relatively high grade of malignancy: swollen astrocytes, with nuclei often bizarre and multinucleated displaced to the periphery. (H & E x 400). (Courtesy of Dr. David Cowen, Columbia-Presbyterian, Neuro-pathology)

standpoint a marked hypercellularity is present with marked variability of cellular and nuclear appearance (*Fig. 27-5*). Multinucleated cells and mitotic figures are frequent (4-5 per high power field). Hyperplasia of blood vessels is very evident (endothelial proliferation). The additional feature of necrosis serves to distinguish this tumor from the anaplastic astrocytoma. The vascular proliferation often results in hemorrhage into the tumor. The vascular hyperplasia of adventitia and endothelium may be so prominent as to suggest actual sarcomatous alteration. Both the hyperplasia of the blood vessel wall and the rapid growth of the tumor often result in a tumor that out grows the blood supply with resultant necrosis within the tumor. Grossly, the presence of hemorrhage and necrosis is evident (*Fig. 27-6*). These features are also evident on CT scans (*Fig. 27-7*), which will demonstrate area of hemor-

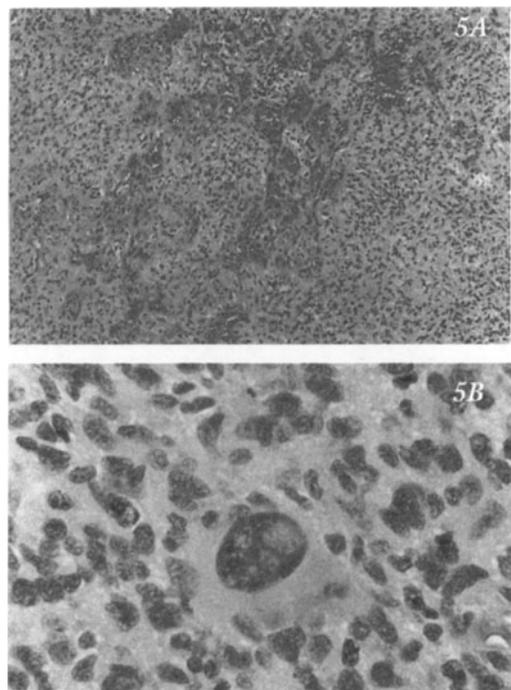


Figure 27-5. Glioblastoma surgical histological features. Case 27-4. Refer to text and Figure 27-7

A) Low powered field demonstrating marked cellularity and marked vascular proliferation with areas of micro-hemorrhage (approximately 100x in original). B) High powered field demonstrating marked pleomorphism; giant cells and mitotic figures (approximately 400x in original).

rhage, necrosis, and edema and with contrast, a considerable degree of ring enhancement.

Prognosis and Treatment: For malignant astrocytomas, surgery may be employed for purposes of decompression and for debulking the tumor mass so that fewer malignant cells remain to be destroyed by radiotherapy. For the glioblastoma, median survival with surgery only is 6 months, with surgery and radiotherapy, 12 months. The role of chemotherapy is uncertain, the percentage of long-term survivors maybe moderately increased. (Refer to DeAngelis, 2001 for additional discussion). In the study of Shapiro et al (1989), 29-37% of patients with glioblastoma receiving radiotherapy survived for 18months Chemotherapy produced minor additional survival (approximately 2-3 months).

In general younger patients with polar lesions who are able to tolerate extensive resection, radiotherapy and perhaps chemotherapy have the longer survivals (Scott et al, 1999). Why do these patients do poorly? Although at times these tumors may arise superficially in the cerebral cortex, more often they seem to originate in the subcortical white matter. They then appear to infiltrate widely through the cerebral

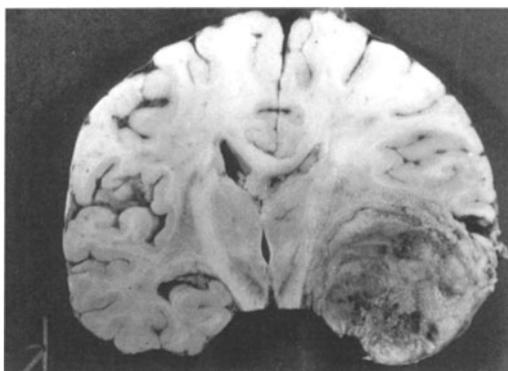


Figure 27-6. Glioblastoma multiforme of the left temporal lobe compressing brain stem and ventricular system. This 43-year-old white male had the onset of short “dreamy” states preceded by a distinctive taste and a sensation of familiarity. Despite a craniotomy and radiation therapy, the patient had a 14-month course characterized by a progressive right hemiparesis, a nominal aphasia, a severe receptive aphasia, increasing disorientation, lethargy, headache, vomiting and papilledema. (Courtesy of Drs. John Hills and Jose Segarra)

hemisphere, often along white matter systems to involve other areas of the brain (e.g., via the corpus callosum to involve the opposite hemisphere). At times, a multi-centric origin may be suspected. Necrosis and hemorrhage are frequent; and progression of neurological deficit is often rapid. At times, the episodes of necrosis and hemorrhage may suggest vascular accidents.

The variable clinical course of a glioblastoma in younger (40 year old) patients has already been presented in chapters 21 and 24. Those cases should be reviewed at this time. The clinical course in an older patient with a 4-5 day course prior to diagnosis, which initially suggested a possible cerebrovascular event, is presented as case 27-4 and in Figures 27-5 &7. In retrospect, it was evident on the CT scan and at surgery that the acute onset reflected the hemorrhage and necrosis, which had occurred

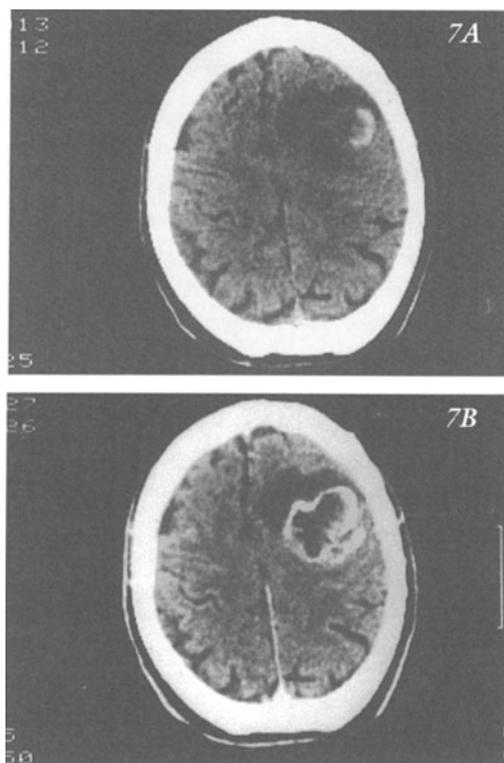


Figure 27-7. Glioblastoma: case 27-4. Refer to text. CT scans A) Non-enhanced CT scan demonstrated a low-density mass in the left frontal parietal parasagittal region, with areas of hemorrhage. B). CT scan (with contrast) demonstrated an irregular rim of enhancement.

within the tumor.

Case 27-4 (patient of Dr. Tom Mullins): This 68 year old right handed white male was admitted to St Vincent Hospital with an apparent 4 to 5 day history of difficulty in doing calculations and in speaking, "he could think of the word, but had difficulty getting it out".

Neurological examination: *Mental status:* Speech was limited to short phrases with loss of connectors and sentence structure. Writing was impaired but repetition, comprehension, naming and reading were intact. *Motor system:* Fine motor movements of the right hand were impaired. Tone was increased on the right. *Reflexes:* The right patellar reflex was increased. Bilateral Babinski signs were present.

Initial Clinical Diagnosis: Diagnosis was uncertain. The abrupt onset suggested possible vascular event such as embolus to the middle cerebral artery but overall pattern including bilateral Babinski sign without significant hemiparesis was unusual.

Laboratory data: *EEG:* Focal left hemisphere delta and theta slow wave activity. *CT scan* (Fig.27-7): A) the *non-enhanced study* demonstrated a low-density mass in the left frontal-parietal parasagittal region with areas of hemorrhage. B) The *contrast-enhanced study* demonstrated an irregular rim of enhancement. *Angiograms* indicated an avascular mass in the left frontal-parietal area

Subsequent course: Dr. Alex Danylevich performed a subtotal resection of this tumor that was found to contain blood clot and cystic fluid. The histology of the tumor was glioblastoma multiforme (Fig. 27-5). The patient subsequently received 4000cGy whole brain radiation and an additional 2000cGy to the tumor site. Three months following surgery, the patient developed increasing obtundation. CT scan revealed a large left frontal necrotic mass. Fever, hypocalcemia and hypernatremia developed and he expired one month later.

Comment: This patient presented with what appeared to be an abrupt onset of language problems raising the question of a cerebrovascular accident. In retrospect, it was evident on the CT scan and at surgery that the

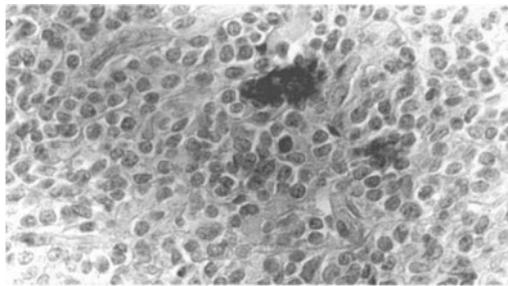


Figure 27-8. Oligodendroglioma. A relatively uniform mosaic pattern of cells with a small nucleus surrounded by a clear halo of cytoplasm is evident. A small area of calcification is present in this field; much larger areas of calcification were evident in other fields. (H & E x 400) (Courtesy of Dr. David Cowen).

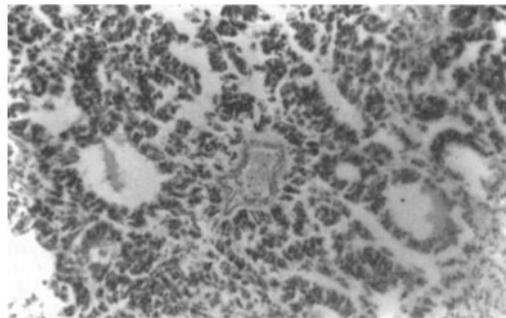


Figure 27-9. Ependymoma of the fourth ventricle. Clusters of ependymal cells are arranged as rosettes or as perivascular pseudorosettes. (H & E x 125) (Courtesy of Dr. John Hills).

acute onset reflected the hemorrhage and necrosis that had occurred within the tumor. This was a rapidly growing, extremely malignant tumor, which apparently had outstripped its blood supply despite the neovascularity.

Other types of glial tumors: oligodendrogliomas: this variety of glioma is found in the cerebral hemisphere of young and middle aged adults constituting 5 –20 % of all glial tumors. The majority is low grade with a long course of 5-15 years; refer to case 18-2. A small percentage are anaplastic or mixed tumors containing anaplastic astrocytoma elements. (Fig 27-8 demonstrates the histology)

Other tumors of neuroepithelial origin: This group contains two very common tumors of the pediatric patient: (1) *Primitive neuroectodermal tumor: medulloblastomas* (Fig.27-9 and case 20-1), and (2) *ependymomas* (Fig.27-

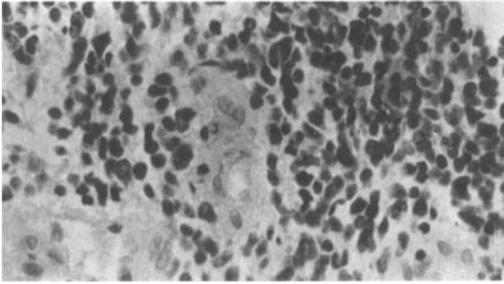


Figure 27-10. Medulloblastoma. Clusters of small cells with densely staining nuclei are present. (H & E x 400) Refer Chapter 20 for illustration of a gross specimen. (Courtesy of Dr. David Cowen).

10). These brain tumors of the posterior fossa constitute the most common solid malignant tumors found in the pediatric population. These tumors have been discussed and illustrated in chapters 13 and 20.

The other 2 tumors in this group are rare (1) *Ganglioglioma or neuroastrocytoma*: now considered to represent the diffuse infiltration by a low-grade astrocytoma among neurons of the cerebral cortex - basal ganglia or diencephalic nuclei. At times, this type of histological picture has been noted in the lesion of tuberous sclerosis. (2) *Pinealomas*: These relatively rare tumors of the pineal have been considered already in relation to the brain stem (Chapter 13). The most common tumor of the pineal region is the germinoma.

OTHER PRIMARY INTRINSIC TUMORS OF NON NEUROEPITHELIAL ORIGIN

(1) *Primary central nervous system lymphomas*: Prior to 1980, primary intrinsic tumors of the nervous system of non-neuroepithelial origin were considered rare. Primary lymphomas of the central nervous system have now assumed increasing importance and are no longer rare. In general these malignant tumors have B cell surface markers and are of the diffuse large cell subtype. They were formerly designated reticulum cell sarcoma or microgliomas. As with glioblastomas, the peak incidence occurs in the 50 to 70 year age range. The increased incidence has occurred in both the immune suppressed (AIDS) and the

immune competent population.

(2) *Tumors of blood vessel origin*: Probably the only true vascular neoplasm intrinsic to the central nervous system is the hemangioblastoma of the cerebellum composed of embryonic vascular elements. Giant aneurysms angiomas or arteriovenous malformations of the brain and meninges are composed of adult vascular elements and are not neoplasms but may have mass effect. Hemangioblastomas are discussed in chapter 20

EXTRINSIC TUMORS

Meningiomas: The most common extrinsic tumor above the tentorium is the meningioma. Meningiomas constitute 20% of all types of brain tumors. Based on the epidemiological data from Rochester Minnesota (Radhakrishnan et al, 1995) meningiomas have a total annual incidence of 7.8 per 100,000 populations but the true incidence of symptomatic meningiomas is 2 per 100,000. Most meningiomas (74%) are asymptomatic and are discovered at autopsy or on imaging studies performed for unrelated problems (Fig. 27-11). Meningiomas are tumors of the adult population 30 to 70 years of age. They are more frequent in females due to the fact that many meningiomas contain estrogen receptors. There is an additional increased incidence in patients with breast cancer, at times providing a diagnostic dilemma. Meningiomas arise from arachnoidal cells embedded in the dura. Normally, arachnoidal villi invaginate into the venous sinuses as arachnoidal or pacchionian granulations but arachnoidal cells may be embedded in the dura. In addition, fibrous and vascular elements are, to a variable degree, also included in these tumors. The variable composition has resulted in a histologic classification according to the following main types:

1. A *syncytial or meningothehal* variety composed of clusters of cells similar to the outer layer of arachnoid arranged in nests or whorls and surrounded by layers of elongated or flattened cells.

2. A *fibrous* variety in which interlacing bundles of fibro-blastic elements predominate.

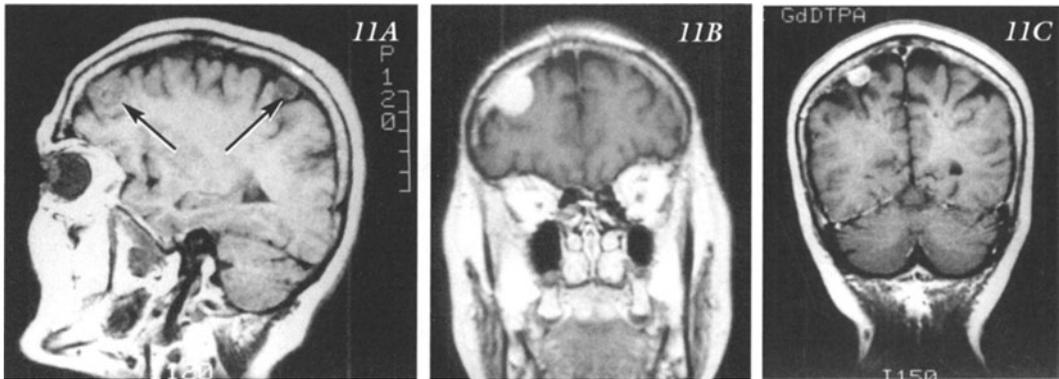


Figure 27-11. Meningiomas: incidental discovery multiple asymptomatic in a 71-year-old ambidextrous female with a normal neurological examination had a history of a transient left posterior thalamic lacunar infarct which was confirmed on subsequent MRI studies. Those studies also disclosed right prefrontal and right parietal asymptomatic meningiomas A) non-enhanced - T1 - right parasagittal section, B) enhanced - T1 - frontal coronal section, C) enhanced T1 parietal coronal section. No changes occurred over the next 5 years.

3. A *psammomatous* variety (probably the most common type) consisting of the same type of arachnoidal cells, arranged in a whorl. In the center of the whorl is an area of hyalinization arranged in concentric lamellae and calcified (psammomatous granules). The calcification is often visible on plain X-rays of the skull.

4. A less common *angioblastic* variety, that appears spongy both on gross and microscopic examination, because it contains multiple small vascular channels. (At times, the term hemangiopericytoma has been applied to this type of meningioma.)

5. A *mixed or transitional* variety. Considerable overlap is apparent as demonstrated in *Figure 27-12*.

It is unclear that these different histologic types have prognostic significance. However a small percentage (7%) from a histologic standpoint have atypical or frankly malignant features of a sarcoma. Regardless of the histologic type, all meningiomas on molecular analysis have a loss of chromosome 22q. A similar defect occurs in patients with neurofibromatosis type 2. These latter patients often have multiple meningiomas in addition to bilateral Schwannomas of the vestibular nerve

These tumors are in general benign and slow growing. Almost all occur external to the brain with a dural attachment - compressing, displacing, and at times invaginating into the brain. Rarely, the tumors may be found with-

out a dural attachment within the ventricle or within the Sylvian fissure. Although not invading the brain the otherwise benign meningioma may invade the overlying bone of the skull. Others excite an osteoblastic reaction in the overlying bone with a marked local thickening of the bone (hyperostosis). What is important about meningiomas is not their histological cell type (sarcomatous degeneration is rare) but their location; in general they are readily amenable to neurosurgical removal. In asymptomatic cases, the risks of surgery may outweigh any conceivable benefit to the patient.

Meningiomas tend to occur in certain specific locations outlined in Table 27-4.

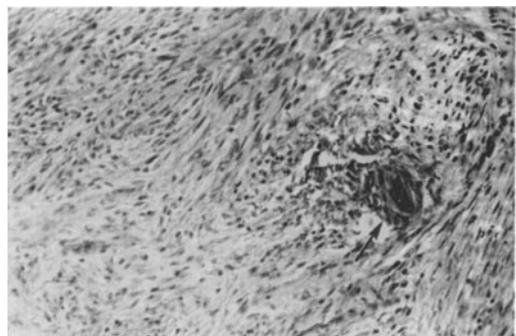


Figure 27-12. Meningioma. Histological appearance of a mixed or transitional type meningioma. Interlacing fibrous bundles and whorls of meningothelial cells are present in addition to a calcified psammoma body (arrow). (H & E x 100) (Courtesy of Dr. David Cowen).

TABLE 27-4 MENINGIOMAS

LOCATION	FREQUENCY*	MANIFESTATIONS
Parasagittal a) Rolandic b) Prefrontal	21-23% (or 33-50%)	Focal motor or sensory seizures or leg weakness (Cases 1-1,18-1), Fig. 27-20 on CD Personality change and dementia (Cases 22- 3)
Lateral convexity	17%	Focal motor seizures hand or face
Sphenoid wing a) Inner third b) Middle third c) Outer third	9-17%	Unilateral exophthalmos and optic nerve atrophy + contralateral papilledema** Bilateral papilledema then inner or outer third findings Temporal lobe seizures (Fig 27-13).
Anterior fossa a) Olfactory groove b) Tuberculum sellae	8-18%	Unilateral anosmia, prefrontal syndrome, dementia (see case 22-4) May mimic pituitary tumor, with compression of optic chiasm, prefrontal syndrome
Posterior fossa	7%	See chapter 13,CP angle, foramen magnum and tentorial syndromes
Other sites a) Intraventricular b) Spinal cord	Not common	Hydrocephalus Spinal cord compression see chapter 9

* Series of Cushing & Eisenhardt (1938), of Courville (1967) and of Taveras and Wood (1964)

** Foster -Kennedy syndrome (See case 23-1)

The course of several meningiomas has been presented already in several of the case histories of Chapter 1, 18, 22 and 23.

TUMORS OF PITUITARY GLAND – see chapter 16 and below.

Other Extrinsic Tumors Involving the Brain Refer to Table 27-5

SECONDARY TUMORS - Metastatic Tumors:

The greatest number of secondary tumors of the central nervous system is spread from a distant site via the blood stream. The majority spread to the cerebral hemisphere or to the cerebellar hemisphere. Metastatic lesions may be solitary or multiple. (Fig. 27-18, 27-19, 27-20). In the series of Delattre et al, 1988, 47% of patients with metastatic lesions to the brain on CT scan had single lesions. These secondary metastatic tumors represent a significant percentage of patients seen with intracranial tumors in a general hospital population. As already noted, 25% of cancer patients have cerebral metastases at autopsy. With increasing

length of survival after the diagnosis of cancer, metastatic spread to both brain and leptomeninges has increased in frequency.

1. The most frequent site of primary tumor is the lung accounting for almost a third of the cases. It has been estimated that almost half of all patients with small cell and non-squamous, non-small cell carcinoma of the lung, at autopsy will have cerebral metastasis (Cox et al 1979).

2. The second most frequent site of primary lesion is the breast. Several examples have been presented in Chapter 21.

3. Certain tumors, which have a lower overall frequency of occurrence than carcinoma of the lung and breast, have a particularly high frequency of metastatic spread to the brain:(a) malignant melanoma (usually multiple), b) hypernephromas (often solitary), and (c) choriocarcinoma. (In the surgical series of Delattre et al, (1988), lung malignancies accounted for 40%; melanoma for 11% and kidney cancer for 11%.)

Treatment Solitary metastatic lesions may be subjected to surgical removal, since median

survival is significantly improved in series where surgery plus radiation is compared to radiation alone: 40 weeks versus 15 weeks (Patchell et al 1990). At other times, when multiple metastasis occur; radiation therapy or hormonal therapy may be employed, with a significant reduction in symptoms (for additional discussion see, Posner 1990, 1992).

Carcinomatous meningitis: Malignant cells are present in the CSF implanting on nerve roots, cranial nerves, hemispheres and meninges (Fig. 27-20, 27-21). Breast cancer, lymphoma, lung cancer and melanoma are the most frequent primary lesions. Hydrocephalus is frequent. Additional discussion and illustrative case histories will be found in Hedges et al 1988. Winkler and DeLaMonte 1987, Gruber and Sobel 1992, Little et al 1974, Olson et al 1974.

Local Invasive Tumors: Direct extension of tumors to involve the brain is less common than metastatic disease. Common primary sites are carcinomas originating in the nasopharynx and nasal sinuses. These tumors may erode the base of the skull or spread through the foramina at the base of the skull to involve cranial nerves such as nerves V and VI. Treatment involves local radiation; results are dependent on the capacity for response of the primary lesion.

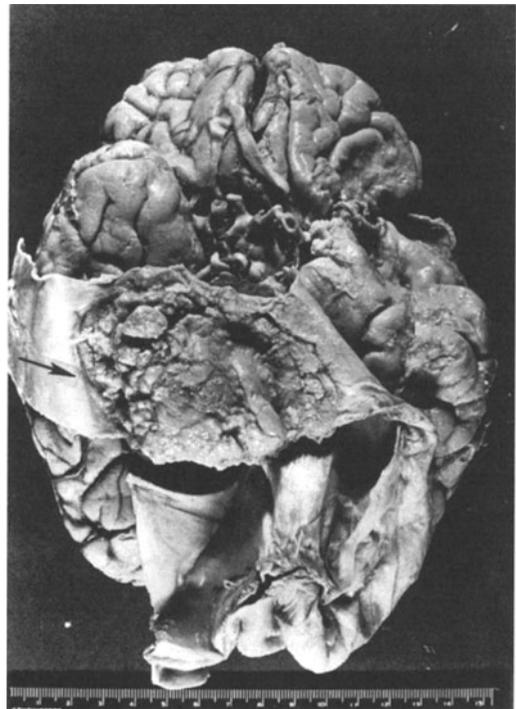


Figure 27-13. Outer third Sphenoid wing meningioma. The dura overlying the sphenoid has been reflected revealing a large meningioma (arrow) compressing the inferior surface of the anterior temporal lobe and adjacent orbital frontal area. This 73-year-old black male had a 14-year history of complex partial and generalized tonic clonic convulsions. (Courtesy Drs. John Hills and Jose Segarra).

The central nervous system may be involved by all of the general types of organisms that infect other systems of the body: bac-

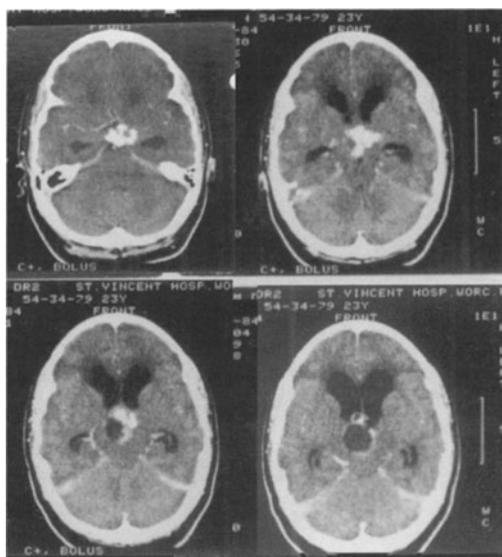
III. INFECTIONS:

TABLE 27-5-OTHER EXTRINSIC TUMORS INVOLVING THE BRAIN

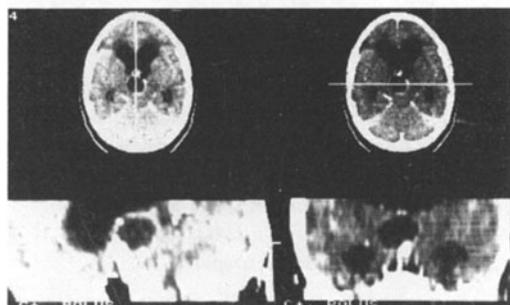
TYPE	LOCATION	STRUCTURES INVOLVED OR MANIFESTATION
Craniopharyngioma	Suprasellar	Pituitary, hypothalamus, optic chiasm (Fig. 27-14)
Epidermoid,	Bone of skull, dura or cisterns	C-P angle or suprasellar
Dermoids/Teratomas	Usually midline	Pineal, pituitary, 4th ventricle
Chordomas	Clivus	Compression of ventral brain stem, basilar artery
Colloid cysts*	F. Monro of Third ventricle,	Acute hydrocephalus with acute headache and coma, often intermittent due to ball valve mechanism (Fig.27-15, 27-16)
Schwannomas**	Posterior fossa:	C-P angle, vestibular nerve most common (see Chap.12)

* The colloid cyst of the third ventricle although uncommon must be recognized in the emergency room, since death may result.

** Except for Schwannomas at CP angle (Fig.27-17), which may also arise from cranial nerves (jugular foramen) and from the sensory nerve roots, all of these tumors are relatively rare. Refer to chapter 13.



14A



14B

Figure 27-14 Craniopharyngioma. A 23-year-old female with a 6-year history of headaches and amenorrhea followed by diplopia and papilledema. Contrast enhanced scan demonstrates suprasellar calcification with large cyst which projects upward into the third ventricle A) thin sections through suprasellar region; B) sagittal and coronal reconstructions.

teria, viruses, rickettsiae, fungi, protozoa, and helminths. Certain organisms do have a predilection for the central nervous system and often for particular segments or certain systems of the neuraxis. Thus, we have already seen that the virus of poliomyelitis involves predominantly the motor neurons of the anterior horn and brain stem. Bacteria such as meningococcus and haemophilus influenzae involve predominantly the meninges. In most instances, when infectious agents involve the central nervous system, they also involve to a variable

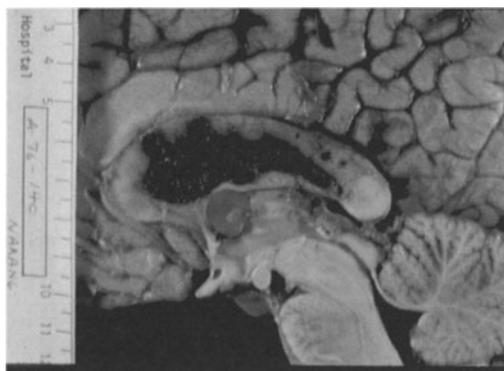


Figure 27-15. Colloid cyst of the third ventricle. This 20-year-old male had sudden attacks of headache; with the last such attack he presented to the emergency room with rapid onset of coma and death.

degree other systems of the body in a general or focal manner. The student should bear in mind that the clinical and pathological manifestations of an infectious disease reflect not only the direct effects of the invading organism but also effects that indicate the body's defensive responses to invasion. Moreover, when immune mechanisms have been suppressed, as in AIDS (acquired immune deficiency disease), organisms that do not usually invade the brain or other organs of the adult patient, may assume major invasive roles. Examples include toxoplasmosis, fungi, cytomegalovirus, etc.

Infections involving the nervous system may be considered under two broad categories:

1. Those infections which involve the central nervous system or subdivisions of the central nervous system in a general or diffuse manner, and
2. Those infections which involve the central nervous system in a focal (or multi-focal) manner

FOCAL INFECTIONS OF THE NERVOUS SYSTEM

The problem of focal infections of the nervous system has an importance far out of proportion to the actual frequency of occurrence of such cases. These focal infections represent, in general, rapidly progressive and compressive space-occupying lesions and they often require emergency neurosurgical intervention.

We have already seen that at the level of

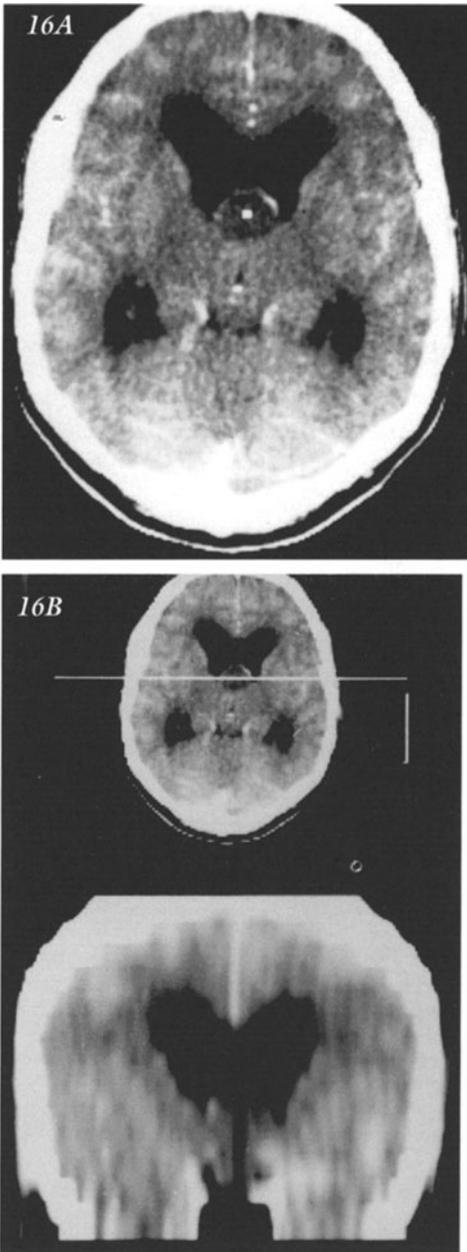


Figure 27-16 Colloid cyst of third ventricle. This 23-year-old right-handed male had a 4-6 week history of generalized throbbing headache and episodic visual obscuration with bilateral papilledema and enlargement of the blind spots. CT scan demonstrated a third ventricular colloid cyst at the level of the foramen of Monro with secondary dilation of the lateral ventricles. A) Contrast enhanced CT at horizontal level just above foramen of Monro. B) Coronal reconstruction. All symptoms disappeared after Dr. Alex Danylevich drained and removed this cyst and shunted the ventricular system.

spinal cord, focal infections are essentially extradural in location. The favorite site of acute focal infection is the fatty tissue of the epidural space. The resultant clinical picture is that of a

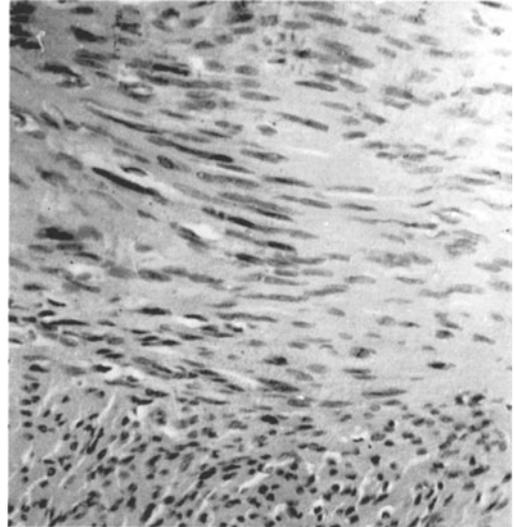


Figure 27-17 Vestibular (acoustic) neuroma or Schwannoma. Microscopic examination of these tumors usually indicates two tissue types: interwoven bundles of spindle-shaped cells with alignment of nuclei in the form of palisades; and looser, somewhat cystic areas. (H & E x 100) (Courtesy of Dr. David Cowen, Columbia-Presbyterian, Neuropathology).

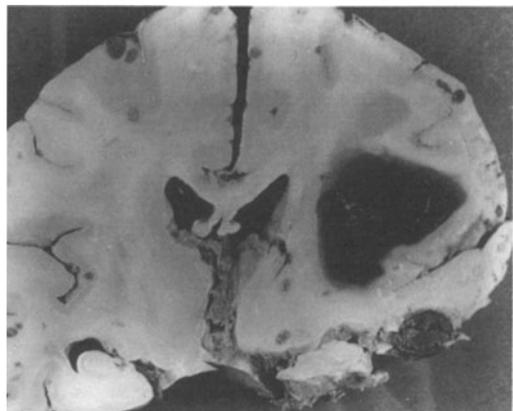


Figure 27-18. Multiple metastatic tumors to cerebral hemisphere from malignant melanoma, with secondary hemorrhage into several of the pigmented lesions in a 40-year-old white female with excision of primary melanoma of the left knee with dissection of the left groin 5 years prior to death. She had multiple cutaneous metastatic nodules despite chemotherapy and then, right temporal headache, nausea and vomiting sudden coma with papilledema and sluggish pupils (Courtesy of Dr. John Hills)

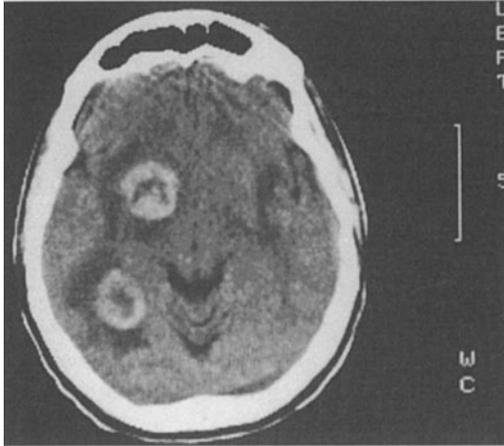


Figure 27-19. Multiple metastatic tumors to brain. CT scans demonstrate multiple high-density lesions with low-density centers, and surrounding areas of edema. Minor enhancement occurred in some of the lesions with contrast. This 43-year-old white male with a 30-pack -year smoking history and a poorly differentiated adenocarcinoma with invasion of peribronchial lymph nodes and of parietal pleura initially presented with hemoptysis. Four months later he presented with a one-day history of confusion, lethargy and frontal release signs and died one month later.

rapidly progressive extradural compressive lesion of the spinal cord. The symptoms and signs are due both to the direct damage from compression and the indirect destruction of tissue produced by vascular compression and occlusion. At the level of the spinal cord also, spinal cord compression, may result from the involvement of and collapse of vertebral bodies by chronic tuberculosis.

ACUTE FOCAL INFECTIONS INVOLVING THE BRAIN

Three syndromes should be considered: 1. Subdural empyema, 2. Purulent brain abscess, and 3. Focal viral cerebritis - h. simplex.

1. *Subdural empyema:* In general, subdural empyema occurs as a result of the direct extension of purulent infection from an adjacent focus of infection in the nasal sinuses or middle ear or following compound skull fractures. The nasal sinuses are now implicated as the major source of infection. Osteomyelitis of the intervening bone is a frequent finding; throm-

bophlebitis of the venous sinuses and of the feeding cortical veins is a not unusual complication. The pus is present in a space that offers

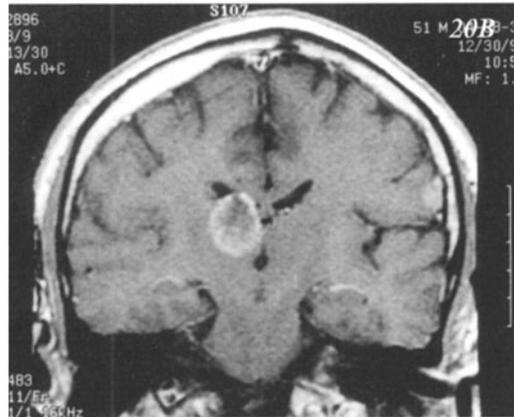
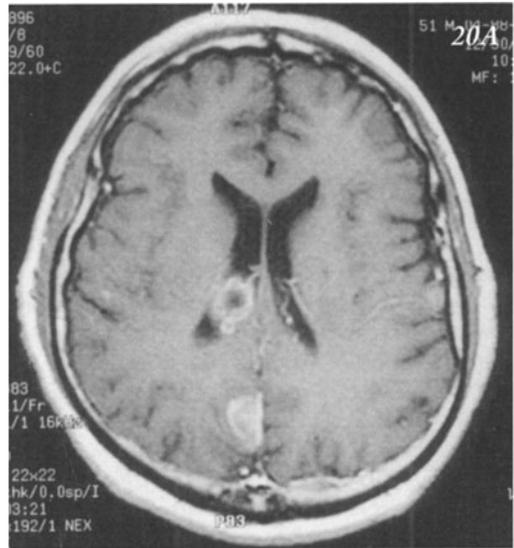


Figure 27-20. Multiple metastatic tumors to brain adjacent to ventricular system and subarachnoid space with carcinomatous meningitis. Which process was the primary one—periventricular solid metastatic lesions or the carcinomatous meningitis remains uncertain. This 51 year old white male teamster had progressive headaches for 6-7 weeks and a 2 week history of a progressive third nerve paralysis. CT scans and MRI scans demonstrated at least 5 distinct areas of contrast enhancing metastatic tumors. CSF contained 90 cells consistent with non small cell carcinoma. Chest x-ray demonstrated a lesion in the upper lobe of the right lung. He received radiotherapy and dexamethasone with improvement in headache. Three weeks later he developed weakness, tingling and depression of reflexes in both lower extremities, plus urinary and fecal incontinence. A) T1 horizontal section. B) T1 coronal section.

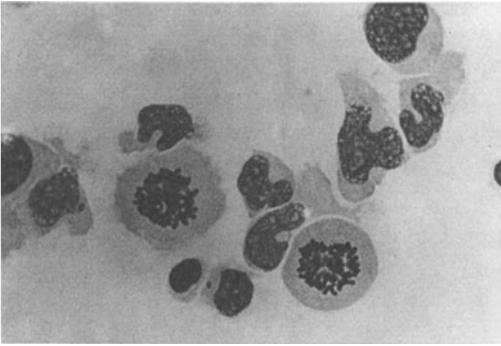


Figure 27-21. "Meningeal Carcinomatosis". Five years after a complete remission from diffuse histiocytic lymphoma (Stage III-B non-Hodgkin's lymphoma), which had presented with symptoms of fever, night sweats, abdominal pain and lymphadenopathy, this 77-year-old female had a biopsy proven recurrence of disease (lymph nodes and bone marrow). She had drowsiness, poor recall, right eyelid ptosis and diffuse weakness of the left lower extremity with tenderness over left femoral and sciatic nerves. Over 2 days she progressed to a complete pupil sparing right third nerve paralysis, incomplete left CN III paralysis (down gaze was preserved), left CN VI paralysis, bilateral peripheral facial paralysis, decreased hearing on left, and bilateral toe extensor weakness. CSF cytology (approximately 1000x) demonstrated large pleomorphic neoplastic cells. The patient received intrathecal chemotherapy (Methotrexate). (Courtesy pathology department St. Vincent Hospital)

very little resistance to the expansion of this purulent mass. The mass is apparently never well encapsulated although in older cases after the removal of the pus, a fibrinous exudate will be found on the inner surface of the dura and the inner surface of the arachnoid. The responsible organism is most commonly the *Staphylococcus aureus*. A sterile secondary inflammation is usually present in the subarachnoid space. This results in spinal fluid findings on lumbar puncture of moderate increases in cells and protein but a normal sugar and negative culture.

Case history 27-5 on the CD presents an example of subdural empyema.

2. Purulent brain abscess. A brain abscess (*Fig. 27-22*) reflects the spread of purulent infection to the brain by several pathways. Direct extension may occur from a nearby focus of infection in the nasal sinuses or mastoid or middle ear. For this reason many soli-

tary brain abscesses tend to be located in the frontal or temporal lobe of the cerebral hemisphere or in the cerebellar hemisphere. Direct introduction of infected material may occur in relation to trauma, e.g., compound skull fractures, or in relation to neurosurgical procedures. Finally, hematogenous spread may occur in patients with a primary source in the lung, in patients with bacterial endocarditis and in patients with cyanotic congenital heart disease where the blood may bypass the screening system of the lungs. Patients with pulmonary arteriovenous fistula are also at special risk. Such hematogenous spread is more likely to result in multiple abscesses rather than a solitary abscess.

Since the introduction of antibiotics, there has been a significant decrease in the number of patients presenting with brain abscess particularly in the number of cases where the abscess is secondary to sinusitis and mastoiditis. Moreover, among the remaining patients there has been a decrease in the percentage of cases with an identifiable primary focus of infection and an increase in cases without an identifiable primary focus. These latter cases may reflect instances where partial antibiotic therapy has eradicated the primary focus but not the brain abscess.

As might be expected, the most common organism is *Staphylococcus aureus*. Streptococci and pneumococci are also encountered as responsible organisms. Rarely, under special circumstances, a fungus infection may be implicated, e.g., mucormycosis in severely debilitated diabetics and aspergillosis in patients receiving immunosuppressive therapy after renal transplantation or in patients with AIDS.

When the cerebral hemisphere is involved the clinical symptoms will correspond to the specific area impacted with focal seizures and rapidly evolving focal neurological deficits as the prominent features.

The electro-encephalogram is likely to show continuous focal 0.5 to 2 cps slow wave activity indicating severe focal damage (refer to *Fig. 2-22*). The CT scan (*Fig.27-23*) will usu-

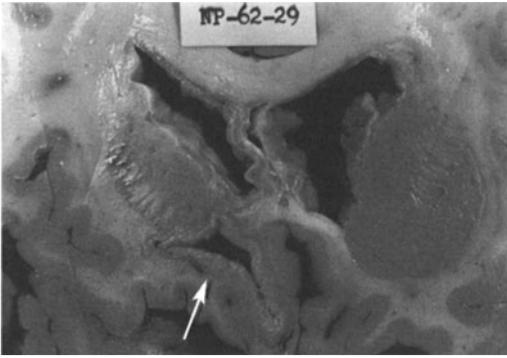


Figure 27-22. Subacute brain abscess (arrow) with associated ventriculitis. This 41-year-old white male, as a child, had a fibroma of the right maxillary sinus that had been treated with surgery and radon implants. Four months before death he developed the first of 4 episodes of meningitis with headache, nuchal rigidity, fever, and chills; cerebrospinal fluid contained 495 white blood cells (75% polymorphonuclear) and a CSF-sugar of 40 mg./100 ml. He had chronic sinusitis of right maxillary and ethmoid sinuses on x-rays and defect in the bone and dura in relation to the right ethmoid sinus. (Courtesy of Drs. John Hills and Jose Segarra).

ally demonstrate a contrast ring-enhancing lesion.

In general the outcome in the untreated brain abscess is fatal. Treatment consists of surgical drainage and total excision of the abscess cavity. In addition appropriate antibiotic therapy must be administered. In the series of Loeser and Scheinberg (1957), surgical therapy in the period 1940-1944 was associated with a 47 percent mortality. By the period 1949-1956, an era of specific antibiotics, this mortality had dropped to 19 percent.

A brain abscess involving the right parietal-occipital area has already been presented in Chapter 23. In reviewing that case, the student should keep in mind that events in a temporal lobe abscess may proceed at a much more rapid pace as regards tentorial herniation with third nerve and brain stem compression.

CHRONIC FOCAL OR MULTIFOCAL INFECTIONS: GRANULOMAS: The followings infections may produce granulomas: tuberculosis, cryptococcus, larva of the pork tape worm (cerebral cysticercosis), toxoplasmosis and schisto-somiasis. In some parts

of the world these infections are a common cause of mass lesions, seizures or hydrocephalus. (See also discussion of AIDS)

GENERAL OR DIFFUSE INFECTIONS: We will consider this section in detail on the CD ROM

This category of diseases is usually presented in detail in microbiology courses and in the infectious disease sections of internal medicine.

a. Those involving primarily the leptomeninges (pia and arachnoid) producing leptomeningitis. Generalized infection of the dura (pachymeningitis) is uncommon. (Fig.27-24, 27-25)

b. Those involving primarily the parenchyma of the brain, producing encephalitis. (Fig.23-26, 27-27)

There are some infections, often viral, that involve both structures producing, a meningoencephalitis.

MENINGITIS (Leptomeningitis)

This is the most common form of infection of the nervous system. The manifestations of meningitis depend on the organism involved, the age of the patient, and the underlying physical status of the patient. Acute, subacute and chronic forms may be considered.

Acute Purulent (Bacterial or Septic Meningitis): This is the most common form of infection of the central nervous system among patients requiring hospitalization. In each case, a specific bacterial organism may be isolated from the cerebrospinal fluid (CSF) in the sub-arachnoid space. In addition, the spinal fluid shows evidence of an acute inflammatory reaction. The fluid is cloudy and under increased pressure with large numbers of white blood cells, predominantly polymorphonuclear leukocytes, e.g., 90 to 98 percent of 500 to 40,000 white blood cells per cubic mm. The CSF sugar content is markedly reduced, relative to the blood sugar. Normal spinal fluid sugar is >50% of the blood sugar. Gram stain of the spinal fluid, latex agglutination tests of CSF and cultures will allow identification of the specific organism. The specific organism and the recommended treatment are indicated in Table

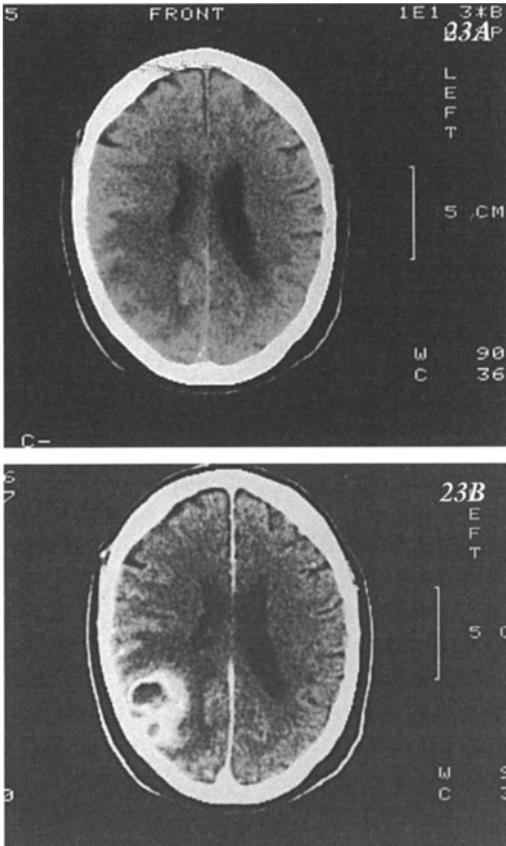


Figure 27-23. Brain Abscess. CT Scan: A) Non-enhanced demonstrates an edematous mass in white matter of right posterior temporal-parietal-occipital areas with compression of the right lateral ventricle. B) With contrast a 3-4 cm ring-like enhancement occurs. This 53-year-old left handed white male with borderline diabetes mellitus had been treated for an abscess in the muscle of the abdominal wall due to anaerobic *Bacteroides* with incision drainage and antibiotics. Seven days later he developed severe “blinding” right sided headaches, confusion, difficulty in reading, word finding, following commands, repetition of short phrases plus flat affect, a neglect of the left visual field and a mild left hemiparesis. All neurological findings resolved over the next 2 days after treatment with antibiotics, dexamethasone and mannitol (to reduce cerebral edema) and immediate evacuation of the abscess. (Courtesy of Drs. Ralph Sama and Bernard Stone)

27-6.

Clinical Presentation: The clinical picture of acute purulent meningitis depends on the age of the patient. An infant under 6 months of age may be febrile, listless and drowsy and may vomit and fail to take feedings. The anterior

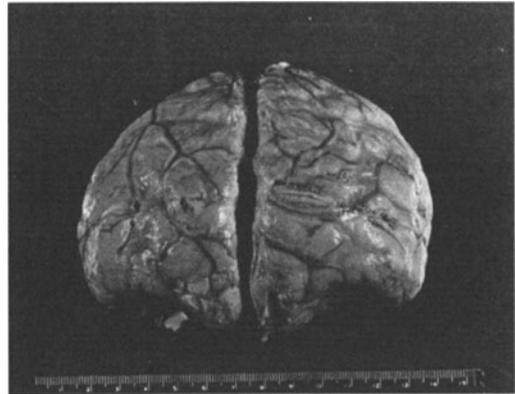


Figure 27-24. Acute meningitis (pneumococcal). This 57-year-old white male had been living in a nursing home with a diagnosis of chronic undifferentiated schizophrenia. Two weeks previously he had become less responsive than usual, then developed a temperature of 104degrees for which he received penicillin. On the day of admission, the patient fell out of bed and became comatose. Cerebrospinal fluid was cloudy with 11,861 with blood cells (80% polymorphonuclears) and a sugar of 36-mg./100 ml. Culture of the cerebrospinal fluid subsequently revealed *S. pneumoniae*. A left and then bilateral fixed dilated pupils developed followed by Cheyne-Stokes periodic respirations, decerebrate posture, and death. At autopsy, the brain was swollen with a yellow-green purulent exudate present in the sub-arachnoid space. (Courtesy of (Drs. John Hills and Jose Segarra)

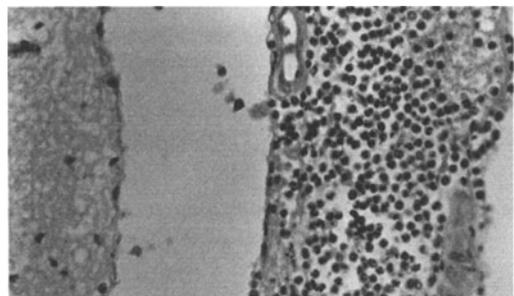


Figure 27-25. Acute meningitis (pneumococcal). The subarachnoid space is filled with inflammatory cells, predominantly polymorphonuclear leukocytes. There has been artifactual detachment of the pia from the cortical surface. (H & E x 400). (Courtesy of Pathology Department, Tufts University School of Medicine).

fontanelle of an infant will be under increased pressure and bulging. An older infant or a child is likely to have nuchal rigidity (resistance to passive flexion of the neck) in addition to fever, convulsions, and coma. A posture of

opisthotonos may be present (extreme extension of head, neck, trunk and limbs).

The older child and adult with meningococcal meningitis will usually have a prodromal period characterized by symptoms of an upper respiratory infection, low-grade fever, and various body aches. With septicemia and, then, the subsequent involvement of the meninges, the symptoms of chills, vomiting, severe headache, and nuchal rigidity occur, often followed by an alteration in consciousness. The signs of central nervous system involvement often appear relatively abruptly. A skin rash is common in the stage of bacteremia. Small or large areas of skin hemorrhage (petechiae and purpura) due to involvement and occlusion of the skin capillaries occur during the process of septicemia and are caused either directly by the organism or indirectly as a result of disseminated aggregation of platelets into small thrombi.

The early recognition of acute purulent meningitis is of importance. If it is untreated, serious intracranial complications develop and death is the usual outcome. Prior to the era of specific antimicrobial therapy, the mortality was close to 90%. With specific therapy, this figure

has been markedly reduced so that the actual mortality in meningococcal meningitis is now 3%, although the mortality in patients with overwhelming meningococemia may still approach 40%. For *S. pneumoniae* the case fatality rate remains high at 21% due to the age of the patients. The case fatality rate for *H.influenzae* is 6 % and for group B streptococcus 7% percent. Eleven to 19% of survivors of meningococcal disease have sequelae usually minor if treated early (peripheral facial weakness, hearing loss), at times major: focal neurological deficit or focal seizures or loss of a limb.

There are several possible complications of meningitis. While these are more likely to occur in delayed or untreated cases, some may occur in those patients receiving adequate treatment. With a marked increase in intracranial pressure (at times, lumbar subarachnoid cerebrospinal fluid pressure at lumbar puncture may be 600 mm. of CSF compared to a normal pressure of 150 mm.) herniation of medial temporal areas through the tentorium may occur with compression of the third cranial nerve and midbrain. A vasculitis may involve blood vessel walls, resulting in occlusion of cortical arteries and veins. The occlusion of corti-

TABLE 27-6:ACUTE BACTERIAL MENINGITIS: COMMON ORGANISMS AT SPECIFIC AGES AND RECOMMENDED TREATMENT

AGE OF PATIENT	BACTERIAL ORGANISMS (on culture)	RECOMMENDED TREATMENT (All are intravenous)
0-1 Month	<i>B. Streptococcus*</i>	Penicillin G (plus in neonates initially gentamicin for 72 hours)
1-23 months	<i>S. Pneumoniae</i> -45%, <i>N.meningitidis</i> -31%	Vancomycin plus a broad-spectrum cephalosporin for <i>S. Pneumonia</i> (see below for <i>N. meningitidis</i>)
2-18 years	<i>N. Meningitidis</i>	Penicillin G**
19-59 years	<i>S. Pneumoniae</i> -60%; <i>N.meningitidis</i> -20%	See above
>60 years	<i>S. Pneumoniae</i>	See above

* Prior to introduction in 1990 of *H.influenzae* conjugate vaccine immunization; most cases were due to this organism. Recommended treatment for *H.influenzae* is ceftriaxone

** For epidemics of *N. meningitidis* in developing countries, a single intramuscular injection of a suspension of chloramphenicol in oil has proven to be effective.

*** Less common agents: *L. monocytogenes* ampicillin + gentamicin,

*** Enterobacteriaceae-broad spectrum cephalosporin +aminoglycoside.

cal veins and superior sagittal sinus may lead to hemorrhagic infarction of the parasagittal frontal parietal areas with a resultant weakness of the lower extremities and focal seizures. In addition, a further increase in intracranial pressure may occur.

As we have already indicated, a thick exudate at the base of the brain (somewhat more likely to occur in pneumococcal meningitis) may damage cranial nerves and also obliterate the subarachnoid cisterns. The end result may be a significant degree of hydrocephalus since cerebrospinal fluid will be unable to pass up over the hemispheres to the areas of absorption. In the child, a progressive enlargement of the head occurs.

Overall, in the recent series of Pomeroy et al (1990), 14% of children had neurological deficits that persisted beyond a year after bacterial meningitis. Of these 10% had only sensory-neural hearing deficits and 4% had multiple neurologic deficits. Seven percent had late, non-febrile seizures. (See also Taylor et al 1990 and Smith 1990).

Treatment: The present recommendations Table 27-7. (Quagliarello & Scheld, 1997, Rosenstein et al, 2001) as to choice of intravenous antibiotics which are to be started based on the Gram's stain of the CSF when the patient is first seen but before CSF or blood cultures are available are presented in Table 27-7.

Once the organism has been identified on cultures or agglutination studies of CSF or blood the recommendation of Table 27-6 should be followed.

Acute Aseptic Meningitis: In these cases, the clinical signs and symptoms of meningitis are present in the sense that the patient complains of headache and stiffness of the neck. Vomiting and nuchal rigidity are present. However these findings are usually less fulminating than those in acute purulent meningitis, e.g., sudden coma and purpura in the adult is unlikely; consciousness is usually well-preserved. The spinal fluid, moreover, is often clear or only minimally cloudy (often described

TABLE 27-7 TREATMENT RECOMMENDATIONS BASED ON CSF STAINS PRIOR TO CULTURE RESULTS

Identification of Agent in CSF (Gram stain) before Culture	Treatment Recommendations (Intravenous)
COCCI	
Gram positive cocci:	Vancomycin plus a broad spectrum antibiotic
Gram negative cocci	Penicillin G
BACILLUS	
Gram positive bacilli	Ampicillin (or penicillin G) plus aminoglycoside
Gram negative bacillus	Broad spectrum cephalosporin plus aminoglycoside
EMPIRICAL APPROACH	
Children <1 month	Ampicillin + broad spectrum cephalosporin and vancomycin
Children >1 month	Vancomycin + cefotaxime or ceftriaxone

as opalescent). A relatively small number of white blood cells is present (5 to 2000 per cubic mm. and usually less than 500 per cubic mm.) in comparison to acute purulent meningitis. Moreover, the white blood cells are predominantly mononuclear (lymphocytes and monocytes). The sugar content of the spinal fluid is normal. Moreover, smears, agglutination studies and bacteriological cultures of the spinal fluid fail to reveal a responsible organism. In general, the causative organism is a virus: ECHO, Coxsackie, non-paralytic poliomyelitis, mumps and lymphocytic choriomeningitis.

The student should note, however, that a similar cerebrospinal fluid reaction may also characterize certain diseases where a secondary meningeal reaction occurs: subdural empyema, brain abscess, and venous sinus thrombosis. At times, a similar spinal fluid formula may be noted in a viral encephalitis. The aforementioned viral agents may, of course, at times present a combined syndrome of meningoen- cephalitis.

Moreover, at times several more significant subacute infections in their early stages may present a predominately mononuclear reaction

in the spinal fluid: tuberculous and cryptococcal (fungal) meningitis. Bacterial organisms will be absent on routine smears and cultures of the cerebrospinal fluid. However, both of these infections are characterized by a low spinal fluid sugar, and appropriate stains and cultures (and in the case of cryptococcal infection specific antigen studies) will eventually disclose the organism. These infections, although not common at the present time, in the non-immunosuppressed population, are of importance because a) specific therapy is required, b) with the increase in cases of acquired immune deficiency syndrome; the incidence of these diseases has increased.

Differentiation of the various types of viral meningitis may be made by specialized immunological techniques for the measurement of neutralizing antibodies. Viral meningitis is a self-limited disease. No specific treatment is available (see below, however, under H.simplex). Recovery is in general complete - unless, the meningitis is an epiphenomenon in the midst of an encephalitis.

Other types such as aseptic, tuberculous, fungal, meningovascular neurosyphilis and other spirochetal infections are considered on the CD ROM

ENCEPHALITIS: This topic is considered in detail on the CD Rom and in general medical texts. See also figures 27-26 and 27-27. A brief introduction is provided here.

The term encephalitis refers to a diffuse invasion of the parenchyma of the brain by an infectious agent.

At the present time, clinical presentation of encephalitis is probably less common than those diseases considered under the category of meningitis. During particular epidemics certain infectious agents involving the central nervous system have produced a large number of cases with encephalitis. However, subclinical or minor diffuse involvement of the central nervous system probably occurs in the course of a number of common viral diseases, primarily as a mild aseptic meningitis or meningo-

encephalitis. Even in epidemics of encephalitis or poliomyelitis, there may be many subclinical cases. For example, for Japanese encephalitis, the ratio of subclinical to overt clinical cases has been estimated at 200 or 300:1 (Monath 1988).

In general, most cases falling into this category reflect viral infection. Evidence of viral particles will be found as inclusions within the cytoplasm or nuclei of neurons. With the exception of the spirochete, bacteria do not produce a diffuse encephalitis, although bacteria may produce multiple areas of abscess formation. Other infectious agents may produce encephalitic involvement of the nervous system. The rickettsiae which are intermediate in size between bacteria and viruses, usually produce signs of a meningoencephalitis in addition to a characteristic skin rash. Examples are typhus, and Rocky Mountain spotted fever). Moreover, certain protozoal parasites may invade the central nervous system producing a subacute encephalitis. Examples include toxoplasmosis and trypanosomiasis (African Sleeping Sickness).

Encephalitis may be acute or chronic. Most cases fall into the acute category; most viral and rickettsial diseases are acute. On the other hand, the spirochetal infection and protozoal infections of the central nervous system are, in general, chronic or subacute processes. Recently, however, several viruses and prions have been implicated in chronic diffuse progressive processes (previously considered to be of an unknown etiology) involving the nervous system.

ACUTE ENCEPHALITIS: ACUTE VIRAL INFECTIONS

The pathology of viral infections of the neural parenchyma involves a viral invasion of neurons with the production of intranuclear or intracytoplasmic inclusions (*Fig 27-27*) and the acute degeneration and destruction of nerve cells. There is a cellular infiltration of neural tissue and an accumulation of inflammatory cells about the degenerating nerve cells, in a perivascular location (*Fig. 27-26*). The cells are usual-

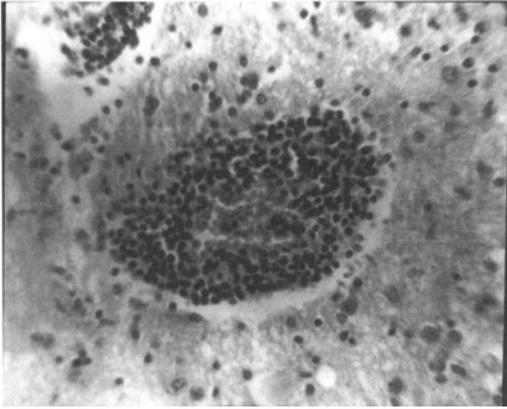


Figure 27-26. Encephalitis (herpes simplex). A significant collection of mononuclear cells is present in the perivascular space with infiltration of adjacent cerebral cortex. This 32-year-old patient had the acute onset of fever, headache, and generalized convulsions. Over a 30-day period, he developed increasing stupor, bilateral extensor plantar responses, and dilated pupils. (H & E \times 320). (Courtesy of Dr. John Hills).

ly mononuclear although in some processes, e.g., acute poliomyelitis or in a severe case of encephalitis, there are often noted a significant number of polymorphonuclear leukocytes at times involved in neuronophagia. A microglia proliferation is often noted in the involved neural parenchyma. To a variable degree adjacent meninges may be infiltrated by inflammatory cells. Depending on the degree of meningeal infiltration and on the severity to which the underlying parenchyma is involved, a variable increase in cells (predominantly lymphocytes) will be noted in the spinal fluid. Occasionally a normal cell count may be present, more often 100 to 500 cells per cubic mm. are present. The protein content is usually increased; the sugar and chloride content are normal.

The differentiation of the particular virus involved depends on:

a. The specific clinical pattern of the disease: some viruses involve particular areas of the central nervous system; some have associated involvement of other organ systems.

b. Virus isolation studies: inoculation of blood, nasal washings, excretions, cerebrospinal fluid, or fresh post-mortem brain tissue into susceptible animals. In some special-

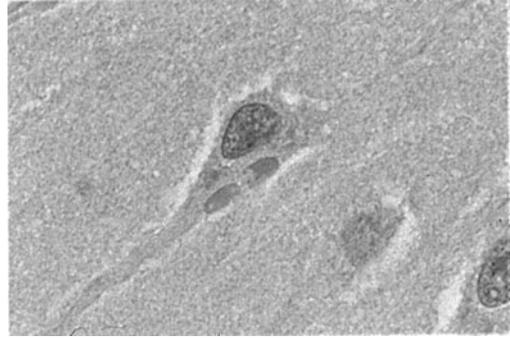


Figure 27-27. Encephalitis. Rabies. Negri bodies are present as cytoplasmic inclusions in neurons of the hippocampus. Intracellular inclusions are characteristic of viral diseases. (H&E 100 \times) (Courtesy of Dr. Thomas Smith)

ized centers, tissue culture techniques may be employed.

c. Application of acute and chronic serological tests to measure antibody levels (complement fixation or antibody neutralization tests).

It had been traditional to divide these viral infections into *neurotropic group* (primary involvement of the central nervous system) and a *non-neurotropic group* (involvement of the central nervous system in humans is usually secondary to or less prominent than involvement of other organ systems). As we will discuss with the herpes group of virus infection, the distinction is to some degree artificial. The infections with the neurotropic may be epidemic (the arthropod borne viruses such as equine encephalitis or West Nile) or non epidemic such as rabies.

A more modern classification divides viruses into those containing RNA and those containing DNA.

Examples of RNA containing viruses include: the enteroviruses (polio, Coxsackie, ECHO), the arboviruses (Eastern and Western Equine, Japanese, etc.) rubella, mumps and measles, rabies and HIV.

Examples of DNA containing viruses include Herpesvirus, papovavirus and pox-rus-virus. An overview of viral encephalitis is provided in the review of Whitley (1990).

Neurotropic Group: Epidemic group: Within the epidemic group several infections

may be grouped together because they share common characteristics: a) Equine encephalomyelitis with Eastern U.S.A., Western U.S.A., and Venezuelan subtypes (Deresiawicz et al, 1997). b) Japanese B encephalitis (probably the most common form. World wide in recent years). c) Russian tick encephalitis. d) St. Louis encephalitis. e) West Nile encephalitis a recent problem in the eastern United States (Nash et al 2001, Tyler, 2001) f) LaCrosse virus encephalitis, probably the most frequent variety in the U.S. in recent years (McJunkin et al, 2001).

In each of these infections a relatively diffuse involvement of the cerebral cortex, diencephalon, brain stem and cerebellum occurs. In each, an arthropod, usually a mosquito, has been implicated as a vector of transmission. A species of bird or mammal has often served as a reservoir of infection. For these reasons, cases have occurred predominantly in a seasonal manner. (In northeastern United States, for example, most cases of Eastern equine and West Nile encephalitis have occurred in the late summer or early fall months, a time when mosquitoes are frequent). Vaccines are available for prevention of some of the more common varieties (Hoke et al, 1988).

The clinical syndrome in most cases is characterized by the sudden onset of headache, vomiting, drowsiness, confusion, convulsions, coma, fever, plus or minus, stiffness of the neck. Evidence is often present on examination of the patient of diffuse and, at times, multifocal involvement at multiple levels of the neural axis: coma, confusion, myoclonic jerks, status epilepticus, decorticate or decerebrate rigidity and cerebellar findings. In some cases, cranial nerve findings, aphasia and hemiplegia, will be present. The duration of the disease is a matter of days to several weeks. *The state presented by the patient may be described as an encephalopathy.* The major differential diagnosis is that of toxic metabolic encephalopathy. A variable mortality occurs in part related to the age of the affected patients. The mortality of Eastern equine encephalitis, which has affected chil-

dren predominantly, has approached 75 percent, with significant residuals in those recovering. *Encephalitis lethargica (Von Economo's encephalitis)* occurred as an epidemic in the period 1916-1926. More recent cases have been described by Howard and Lees (1987). A viral etiology was suspected but never confirmed: the means of transmission remained uncertain. This infection differed from the previously described varieties of encephalitis in the sense that although diffuse, the pathology tended to be concentrated in a periventricular location with severe involvement of structures bordering the aqueduct and third and fourth ventricles. The periaqueductal region and other structures of the midbrain were particularly affected. Reflecting the significant involvement of the midbrain and of the associated structures of the extrapyramidal system, disorders of eye movement and movement disorders of various types were prominent; in addition to the more general symptoms of lethargy, headache and fever. Since the involvement of the cortex was less severe, seizures and focal cortical deficits were less frequent. The mortality approached 25%. Among those who survived, post encephalitic residuals were common. In contrast to other forms of encephalitis, Parkinson's disease and other disorders of extrapyramidal function were frequently noted; the Parkinson's disease usually appeared to emerge or evolve as a symptom after the clearing of the acute symptoms (see chapter 19).

Acute anterior poliomyelitis, the other member of this epidemic group of neurotropic viruses, has already been discussed in relation to the spinal cord. The portal of entry is the gastrointestinal tract. The central nervous system is involved either by spread along the axis cylinders or via a generalized viremia. The virus involves predominantly the large motor neurons of the anterior horn and of the brain stem with lesser involvement of other neurons in the spinal cord.

Non epidemic neurotropic virus infections

The two most familiar members of this group - Herpes zoster (discussed previously) and rabies - do not have their major effects at

the level of cerebral cortex.

Rabies: The virus of rabies is present in the saliva of rabid animals and invades the central nervous system several weeks to months after a bite from an infected animal (dog, cat, wolf, fox, raccoon, squirrel, or bat). The virus travels to the central nervous system along peripheral nerves. The symptoms relate to the characteristic involvement of nuclei of the brain stem, Purkinje cells of the cerebellum, and pyramidal cells of the hippocampus (Ammon's horn). In addition, there is a significant inflammation and necrosis of the spinal cord or brain stem at the segmental site corresponding to the radicular dermatome involved by the bite. The cerebral cortex is relatively intact and consciousness is preserved.

The initial symptoms consist of numbness and tingling in the distribution of the involved peripheral nerve, followed by headache, vomiting and a stage of agitation. This latter stage is characterized by restlessness, generalized convulsions, and at times, visual and auditory hallucinations. Marked alteration in emotions occurs: unreasonable fear, rage and depression. In this stage laryngeal and pharyngeal spasm (with fear of water, "hydrophobia") is prominent. In a later stage of flaccid paralysis, impairment of vocal cords and of respiratory centers develops. In approximately 20 percent of cases, an ascending flaccid paralysis dominates the acute stage (Plotkin and Koprowski, 1978).

Death occurs within 2 to 5 days of onset of central nervous system symptoms. At autopsy, the diagnosis may be established in man or other infected animals by the findings of characteristic acidophilic (eosinophilic) inclusions (Negri bodies) within the cytoplasm of hippocampal pyramidal cells (Fig.27-27).

Because of the long incubation between exposure to the virus and the development of neurological symptoms, prophylactic treatment is possible. Thus, the administration of a vaccine containing the attenuated virus (first introduced by Pasteur), induces the production of anti-bodies, and may prevent the development of neurological symptoms. The combination of this active immunization with pas-

sive immunization with antiserum containing antibodies to rabies has been demonstrated to be much more effective. The current vaccine is the human diploid cell vaccine, the current antisera - human rabies immune globulin. Previous treatment protocols involving nervous system derived vaccines resulted in post vaccinal demyelinating reactions. Once symptoms have developed, no effective treatment is available. In under developed areas of the world a high mortality occurs. (see Baer & Fishbein 1987 and Fishbein & Robins, 1993 for a review of epidemiology and current concepts of treatment.).

Non-Neurotropic Viral Infections:

These viruses were traditionally considered as not producing significant symptoms of central nervous system involvement. Indirect evidence suggests that some of these viruses (mumps, measles, enterovirus) do invade the central nervous system in a much greater percentage of otherwise asymptomatic cases. In some of these diseases, e.g., herpes simplex, there is evidence of direct invasion of the central nervous system when the syndrome of acute encephalitis occurs. In other viral infections, e.g., mumps and measles, it is often unclear when central nervous system symptoms develop, whether one is dealing with an actual viral invasion of the central nervous system producing an acute encephalitis (direct invasion of neurons), or whether one is observing an immunological reaction to infection elsewhere producing an acute allergic post-infectious encephalomyelitis, (white matter predominantly involved with perivenous demyelination).

Types Of Non-Neurotropic Viral Infections:

1. *The herpes virus family:* included herpes simplex, herpes zoster/varicella, cytomegalovirus and Epstein Barr.

The *Herpes simplex virus (HSV)* has two types - *Type 1* associated with the common cold sore of the lip or oral cavity, often activated by fever and *Type 2* genital herpes with labial vagi-

nal and penile infection. In both instances, the virus remains in a latent form in neural ganglia. (Baringer and Swoveland, 1973), particularly the trigeminal ganglion in the case of Type 1 HSV and the sacral ganglia in the case of Type 2 HSV.

Type 1 HSV is the most common cause of non-epidemic; sporadic acute encephalitis in the United States. The early signs of headache and fever are followed by the development of signs that suggest involvement of limbic structures one or both temporal lobes, and at times orbital frontal (*Fig.30-1*). The virus apparently gains access to the central nervous system by infecting structures that are related to the olfactory system, perhaps by axonal transport along the olfactory bulb and its anatomical connections. In some cases spread may be hematogenous (see review of Picard et al ,1993). Personality and behavioral changes may be present for days or a week; followed by seizures , hemiparesis and aphasia. Rapid or subacute progression to a stage of increasing coma then occurs. In a small number of cases, the patient may present with an overwhelming rapidly fatal state characterized by repeated generalized convulsions; myoclonic jerks of the extremities, decerebrate rigidity, coma and periodic complexes in the EEG. In contrast in a small number of cases, the clinical picture is that of a progressive subacute dementia and confusional state. The CSF demonstrates increased pressure, and a variable number of mononuclear cells plus or minus a variable small number of red blood cells. The electroencephalogram may provide evidence of focal or bilateral temporal lobe abnormalities, including slow waves. At variable points in the disease course, the radioactive brain scan, contrast enhanced CT scan or MRI will demonstrate focal or bilateral temporal (and frontal) abnormalities : enhancing necrotic lesions with considerable edema. Sequential serological studies of blood and CSF may be useful in the diagnosis. The treatment of choice is intravenous acyclovir which can be administered without serious side effects. The response to treatment is directly related to how long the symptoms have been

present and to the level of consciousness. Therefore, if the diagnosis is strongly suspected on clinical grounds - treatment is begun as soon as possible, even though the ancillary laboratory studies are not yet confirmatory. In most instances, a brain biopsy is not obtained unless the patient fails to respond to therapy. Even with acyclovir therapy, 53% of patients will die or will be severely impaired. (See discussions of Hanley, 1990; Whitley, 1992).

Type 2 HSV in adults is associated with an aseptic meningitis or with severe radicular symptoms involving the sacral segments. The latter may include urinary retention (Caplan et al, 1977).

Type 2 HSV infection in the infant or fetus results in severe disseminated disease with multi-system involvement of brain and viscera.

2. *Paramyxovirus* group includes mumps and measles. In the child and adult mumps encephalitis is rare. In the fetus and neonate, mumps virus infection has been implicated as a possible cause of aqueductal stenosis producing hydrocephalus (see Johnson and Johnson 1969).

Measles virus infection may be associated with a variety of central nervous system syndromes including:

- a. an acute or subacute encephalitis
- b. a post infectious encephalomyelitis
- c. subacute sclerosing pan-encephalitis: (SSPE) a form of progressive chronic encephalitis manifested by dementia, ataxia, seizures and myoclonus. The disease usually develops - in a delayed manner after an early childhood measles infection. There is a reactivation of the measles virus within the CNS.

3. *Retrovirus - Human Immunodeficiency Virus (HIV-1)*: This virus infects cells of the immune system (e.g., T helper lymphocytes) - producing an acquired-immune deficiency state (AIDS). Carriers who may be in an early or asymptomatic stage of the disease outnumber actual cases of AIDS or AIDS-related complex (ARC). In the United States during the 1980s specific groups were at high risk: (a) homosexual or bisexual men (66%); (b) intravenous drug users (17%); (c) heterosexual -

sexual partners of patients with AIDS (4%); (d) recipients of blood and blood products (3%); and (e) combined risk - homosexual or bisexual male - also drug user (8%)¹. By the year 2001, Sekowitz quoted figures of 36 million people world wide infected with HIV, with an additional 21.8 dead of AIDS. Approximately 70% of cases occur in sub-Saharan Africa where there are two types of epidemics : 1) a horizontal transmission in adults spread primarily by heterosexual contact and to a lesser degree by shared needles and 2) a vertical transmission ,infected mothers give birth to infants who have been infected in utero. Significant numbers of cases are also occurring in the Caribbean, southeast Asia, and South America.

The nervous system is involved in at least 60% of patients with clinical disease: The infections may be generalized or focal due to the immunodeficiency state. Thus, there is an increased incidence of cryptococcal fungal meningitis (10%) and of toxoplasmosis granuloma (5%). A high percentage of patients (>30%) have a direct invasion of the CNS by the virus producing a subacute encephalitis referred to as AIDS dementia or HIV, meningitis. In patients with acute HIV-1 infection 24% have an aseptic meningitis.

Other infections of the nervous system (spirochetes, fungi, protozoa, and tuberculosis) will be considered on the CD ROM.

IV. SYSTEM DISORDERS: The following section is included in detail on the CD ROM and in general medical texts. The following subsections are included:

A. Degenerations: These disorders are considered in the chapters on muscle, peripheral nerve, spinal cord, basal ganglia, cerebel-

lum and memory systems. Refer to CD ROM for an approach to classification.

B. Nutritional disorders: Refer to the CD ROM Table 27-8 and to general medical texts

C. Toxic Disorders: These are considered in detail on the CD ROM and in general medical texts. Heavy metals effects are summarized in Table 27-9 Various central nervous systems pharmacologic agents taken in excess may all produce effects on CNS function. Some such as sedatives, anticonvulsants, benzodiazepines or narcotics may produce depression of cognitive function and or ataxia and eventually in severe overdose coma. Neuroleptics may produce extrapyramidal effects. Hallucinogens and amphetamines may produce a psychosis. Use of the latter may be associated with hemorrhagic strokes Cocaine may produce arrhythmias and stroke. Carbon monoxide may produce headaches or coma.

C. Complications of Endocrine disorders: see CD ROM regarding diabetes, thyroid disease, pituitary hormones etc.

D. Remote effects of malignancy: see CD ROM and chapter 21

V. DISORDERS OF MYELIN: Refer to CD ROM. See also Chapters 9 and 13. Figures 27-28 and 27-29 demonstrate cases with clinical involvement of the cerebral hemispheres.

¹ *These percentages vary markedly in different geographic areas and in different population groups. Heterosexual cases are increasing significantly among drug users or their contacts and in Africa, South America and Southeast Asia. New cases among homosexual males are decreasing.*

TABLE 27-8: NUTRITIONAL AND RELATED DISORDERS OF THE NERVOUS SYSTEM*

STRUCTURES INVOLVED	VITAMIN (S) DEFICIENT	MANIFESTATIONS
Cerebral Cortex	-Niacin	-Pellagra: dementia, dermatitis, diarrhea
	-Pyridoxine	-Seizures (possibly of hippocampal origin)
	-B12	-Dementia
Corpus callosum	Specific unknown, possibly toxic, described initially with excess of Italian red wine. Possible role of thiamine.	Marchiafava –Bignami disease: dementia and apraxia. May be seen in patients who also have Wernicke-Korsakoff syndrome.
Diencephalon and brainstem and cerebellum-Periventricular	-Thiamine	Wernicke-Korsakoff syndrome (Ch. 30)
Pons	Specific unclear but does follow too rapid correction of hypo-natremia	Central pontine myelinolysis. Patient is mute, spastic and akinetic (Chapter 13)
Cerebellum	Thiamine or multiple B	Alcoholic cerebellar degeneration (Ch. 20)
Spinal cord	B12	Combined system disease (Ch.9)
Peripheral nerves	Thiamine, or pyridoxine or B12 or multiple B	Nutritional mixed sensory neuropathy or with thiamine beri-beri.
Optic nerves	Thiamine, B12, riboflavin	Optic neuropathy (retrobulbar neuropathy usually bilateral)

- Muscle may also be involved in an alcoholic myopathy-specific unknown but multiple B suspected.
- In infants and children deficiencies of proteins and fat may retard development of nervous system.

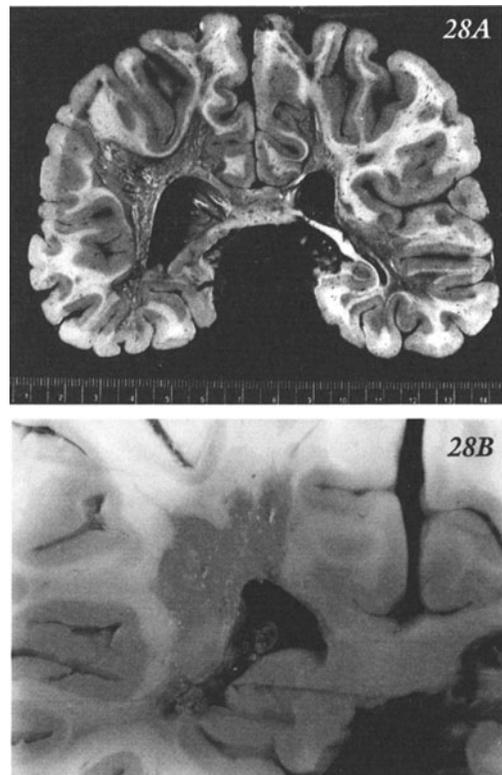


Figure 27-28. Multiple sclerosis: cerebral involvement. A) Severe involvement of the cerebral white matter has occurred, with multifocal gray sclerotic lesions as well as large confluent lesions in a periventricular location. The large confluent lesions and the relative sparing of the arcuate fibers is reminiscent of Schilder's diffuse sclerosis. Destruction of axons, as well as of myelin, has occurred in the larger lesions. This patient had the onset of multiple sclerosis at age 26 and had a progressive course so that by age 30, the patient was essentially bedridden with paralysis of all four extremities, marked impairment of vision, and marked internuclear ophthalmoplegia, and by age 33 had a severe dementia. B) A more typical area of demyelination in the periventricular subcortical white matter is demonstrated in this coronal section from another case of multiple sclerosis. (Courtesy of Dr. John Hills).

TABLE 27-9: EFFECTS OF HEAVY METALS ON THE NERVOUS SYSTEM

METAL	ACUTE AND HIGH LEVEL	CHRONIC LOW LEVEL
Lead	Encephalopathy: acute cerebral edema	In adults: motor peripheral neuropathy In children long term retardation of cognitive function/intelligence quotient
Inorganic mercury	Acute gastrointestinal, renal and hematologic effects	Cerebellar degeneration and the "mad hatter syndrome": dementia and psychosis
Organic mercury	Blindness, cerebral, cerebellar, pyramidal, and anterior horn cell degeneration primarily affecting fetus infants and children (Minimata Bay in Japan etc)	
Arsenic	Acute hemorrhagic encephalopathy	Peripheral neuropathy: sensory/motor
Copper		Hepatolenticular degeneration: Wilson's Disease -genetic defect- (Chap.19)
Manganese		Parkinson's disease

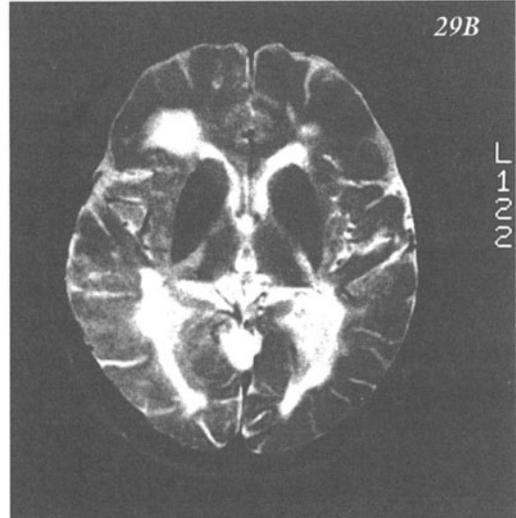
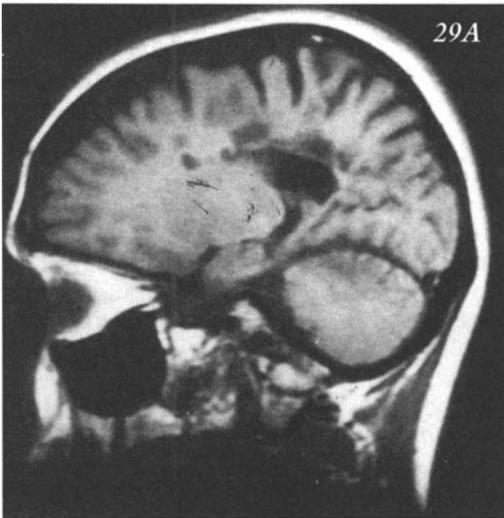


Figure 27-29. Multiple sclerosis. MRI scans. This 38 year old white female bank employee had a 15 year history of relapsing-remitting secondarily progressive multiple sclerosis initially affecting spinal cord (Lhermitte's sign), then optic nerves, then cerebellum and cognitive function. CSF indicated an IgG index of 2.42 (normal 0.45 + 0.1) with 3 oligoclonal bands (normal < 1). In the 5 years following this MRI, she developed dementia and a bedridden state. A) T1 sagittal section. B) T2 horizontal section.