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FOR STUDENTS OF MEDICAL FACULTY

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Учебное пособие по неврологии и нейрохирургии подготовлено в соответствии с типовой учебной программой по неврологии и нейрохирургии для студентов лечебного факультетов медицинских университетов, утвержденной Министерством здравоохранения Республики Беларусь в 1998 году.

В учебном пособии представлены ключевые разделы общей и частной клинической неврологии, а также нейрохирургии, которые имеют большое значение в работе врачей общей медицинской практики и системе неотложной медицинской помощи: заболевания периферической нервной системы, нарушения мозгового кровообращения, инфекционно-воспалительные поражения нервной системы, эпилепсия и судорожные синдромы, демиелинизирующие и дегенеративные поражения нервной системы, опухоли головного мозга и черепно-мозговые повреждения.

Учебное пособие предназначено для студентов медицинского университета и врачей-стажеров, проходящих подготовку по неврологии и нейрохирургии.

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ABBREVIATIONS

ADC	Activated diffusion coefficients
AIDS	Immunodeficiency syndrome
AVM	Arteriovenous malformation
BDNF	Brain-derived neurotrophic factor
CBF	Cerebral blod flow
CCF	Carotid-cavernous fistulae
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computed tomography
DWI	Diffusion-weighted imaging
EEG	Electroencephalography
EMG	Electromyogram
ESR	Erythrocyte sedimentation rate
GCS	Glasgow coma scale
HBO	Hyperbaric oxygen
HMSN	Hereditary motor and sensory neuropathies
ICH	Intracerebral haemorrhage
ICP	Intracranial pressure
MLF	Medial longitudinal fasciculus
MRI	Magnetic resonance imagine
MRN	Magnetic resonance neurography
MS	Multiple sclerosis
NCS	Nerve conduction studies
NGF	Nerve growth factor
PCNSL	Primary CNS lymphoma
PNET	Primitive neuroectodermal tumor
SABP	Systemic arterial blood pressure
SAH	Subarachnoid haemorrhage
SIADH	Syndrome of inappropriate secretion of antidiuretic hormone
SLE	Systemic lupus erythematosus
SMA	Supplementary motor area
SSEP	Somatosensory evoked potential
STN	Subthalamic nucleus
TBI	Traumatic brain injury

MOTOR SYSTEM AND MOTOR DISORDERS

The spinal cord anterior horn cells are influenced by descending pathways from the cerebral cortex and from brainstem centres. These motor cortical and brainstem outflow areas are regulated by other cortical areas, the basal ganglia and cerebellum. The basal ganglia and the cerebellum are both characterized by parallel processing of inputs from cortical areas and subsequent projection back to cortex via thalamic relay nuclei.

MOTOR CORTEX

There are several motor cortical areas in the human; these are classified simply as the primary motor cortex, lateral pre-motor cortex, supplementary motor area (SMA), and motor regions of the cingulate cortex.

The primary motor cortex (Brodmann's area 4) pyramidal cells are the principal source of the pyramidal tract but also project to other motor cortical areas and to sensory cortex, the thalamus, the basal ganglia (corpus striatum), the red nucleus, brainstem reticular nuclei, and the cerebellum (via the corticopontine fibres and pontine nuclei). The primary motor cortex shows a somatotopic organization but pyramidal cells may activate more than one muscle and a muscle may be affected by pyramidal cells spread over a wide cortical area. Primary motor cortex cells are activated prior to and during voluntary contralateral movement, as shown by functional imaging and neurophysiological event-related recordings. Lesions of the primary motor cortex are associated principally with deficits of small accurate finger and hand movements. Such movements require motor cortex outputs not only to agonist muscle spinal motor neurons but also those needed to regulate the activity of antagonists and muscles needed to stabilize proximal joints.

The lateral pre-motor cortex (the lateral part of Brodmann's area 6) is located on the lateral aspect of the frontal lobe, anterior to the primary motor cortex. There are two discreet motor areas (superior and inferior) within the lateral premotor cortex with separate motor cortical maps and corticospinal projections. There is a considerable output from the lateral pre-motor cortex to the medial brainstem tegmentum which projects to the spinal cord in the ventromedial descending system (see below). The pre-motor cortex is important for the control of axial and proximal limb movements and also for the control of movements in response to external cues or instructions. The activation of the lateral pre-motor cortex begins prior to the execution of movement, suggesting an important role in preparation for movement, and may be bilateral. Lesions of the lateral pre-

motor area produce proximal limb weakness and impairment of movements requiring use of the whole arm and hand. There is also impaired learning of motor responses to external cues.

The SMA (medial part of Brodmann's area 6) is on the inner aspect of the frontal lobe, anterior to area 4 and continuous with the lateral pre-motor cortex. The SMA receives considerable basal ganglia inputs and has outputs to the primary motor cortex, corticospinal tract, basal ganglia, cerebellum, red nucleus, and reticular formation. Like the lateral pre-motor cortex, the SMA seems to be important for the preparation of movements, particularly internally generated, learned, sequential, or bimanual movements. SMA lesions lead to difficulty initiating speech and movement, impaired bimanual co-ordination, and the 'alien limb' phenomenon where the arm moves spontaneously in response to external stimuli, grasping at objects spontaneously. This may represent a dissociation of externally (lateral pre-motor cortex) and internally (SMA) cued movement.

Cingulate motor areas have been identified in humans and non-human primates. They have outputs to spinal cord and the basal ganglia and receive inputs from frontal pre-motor cortex. Cingulate motor neurons are active in internally generated movements and cingulate activation is seen mainly with complex motor tasks. Stimulation of cingulate cortex produces complex motor activity.

The descending pathways

The descending pathways are grouped into two divisions within the spinal cord. A dorso-lateral group contains the lateral corticospinal tract along with the rubrospinal tract and the crossed reticulospinal tract (from the lateral pontine tegmentum). These dorso-lateral pathways are concerned with distal movements. The ventro-lateral group is made up of the ventral corticospinal tract with the interstitiospinal, vestibulospinal, and reticulospinal (from medial pontine and medullary tegmentum) tracts and is involved in the control of proximal movements.

The pyramidal tract comprises the corticobulbar and corticospinal tracts and in the human, the latter component contains about one million fibres on each side. About 60 per cent of the fibres in the corticospinal tract originate in the frontal motor areas. The remainders are from parietal and somatosensory cortex. The corticospinal tract influences spinal afferent pathways, inhibitory interneurons, and gamma efferent cells as well as the alpha motor neurons. There is considerable convergence and divergence within the corticospinal tract; cortical pyramidal cells project to several muscles and each muscle can be activated by cells from a large cortical motor field. Direct synapses with alpha motor neurons are particularly dense on cells concerned with finger movements and there is a close association between the corticospinal tract and the execution of fine finger movements. Lesions of the pyramidal tract tend to produce impaired manual dexterity with variable degrees of weakness.

Other descending pathways are poorly understood in man. The reticulospinal pathway appears to be important in the startle reflex. Vestibulospinal pathways are concerned in part with postural control.

THE CEREBELLUM AND BASAL GANGLIA

Neither the cerebellum nor the basal ganglia have direct efferent connections to the spinal motor apparatus and yet both are clearly involved in the correct execution and control of movement. Profound disturbances of movement as their primary symptoms we can find in patients with lesions of these structures. Anatomically, both structures are characterized by extensive inputs from the cerebral cortex, parallel internal circuitry, and projections back to the cortex via thalamic relay nuclei. Despite much information about the anatomy and cellular neurophysiology of the cerebellum and basal ganglia, their precise functions are not clear.

The cerebellum

The cerebellum is made up of two hemispheres separated by a midline vermis. There are three lobes, the anterior, posterior, and the flocculonodular lobe. There are three deeply situated outflow nuclei in each hemisphere, the fastigial nucleus medially, the interposed (made up of globose and emboliform), and the dentate nucleus laterally. The majority of cerebellar efferents leave via the superior peduncle. The inferior and middle peduncles are largely composed of afferent fibres from the spinal cord and brainstem nuclei. Within the cerebellum there are three phylogenetic regions:

1. The neocerebellum (pontocerebellum) includes the bulk of the cerebellar hemispheres and the central portion of the vermis. It receives the bulk of the pontine inputs via the middle peduncle. The neocerebellum is principally concerned with the co-ordination of the ipsilateral limbs.

2. The paleocerebellum (spinocerebellum) consists of the parafloccular lobes and the remainder of the vermis of the anterior and posterior lobes. It receives direct inputs from the spinal cord via the inferior peduncle and is probably concerned with the regulation of muscle tone.

3. The archicerebellum (vestibulocerebellum) is composed of the flocculonodular lobe only and receives direct vestibular inputs via the inferior peduncle.

In fact, there is considerable overlap in the connections of these three regions and their separation on the basis of their inputs is only approximate. The cerebellum may also be subdivided on the basis of outflow projections. The lateral mass of each hemisphere projects to the dentate nucleus, the vermis projects mainly to the fastigial nucleus and an intermediate zone sends fibres to the in-

terposed nucleus. The flocculonodular lobe, vermis, and certain hemisphere areas also project to the vestibular nuclei. Another interesting feature of cerebellar organization concerns sagittal strips of cortex which share inputs from the same regions of the olivary nuclei.

Afferents

All cerebellar afferents terminate in both the cortex and the cerebellar nuclei. The cerebellar afferent systems are as follows.

The vast majority of cerebellar afferents are from the pontine nuclei, through the middle peduncle. These nuclei relay cortical inputs to the cerebellum from the ipsilateral frontal and parietal lobes. These are not collaterals of motor corticospinal fibres. The pontocerebellar projection is to most areas of the contralateral cerebellum and the interposed and dentate nuclei. Pontocerebellar afferents form mossy fibres within the cerebellum, synapsing in the granule cell layer of the cerebellar cortex and in the cerebellar nuclei.

Direct spinocerebellar input is via the inferior peduncle along with afferents from the vestibular and brainstem reticular nuclei. These also enter the cerebellum as mossy fibres.

The inferior olivary nucleus receives inputs from the spinal cord, cerebral motor cortex, and brainstem. It sends climbing fibres directly to cerebellar Purkinje cells and the cerebellar nuclei.

Direct aminergic inputs arise from the locus coeruleus (noradrenergic), raphe nuclei (SHT), and midbrain ventral tegmentum (dopaminergic). These project directly to Purkinje cells.

Cerebellar cortex

There is a complex somatotopic representation in the cerebellar cortex which can only be detected in anaesthetized animals. There appear to be two maps, one in the anterior lobe and one in the posterior lobe. Midline structures are represented in the vermis and limbs laterally in the hemispheres.

The circuitry of the cerebellar cortex is located in three cortical layers; the superficial molecular layer, the Purkinje cell layer, and a deep granule cell layer. Afferents arrive as either mossy or climbing fibres (except for the small number of aminergic afferents) and all efferents are Purkinje cell axons which terminate in the cerebellar or vestibular nuclei. There is some evidence that the firing characteristics of the Purkinje cells are altered by the pattern of climbing and parallel fibre activation, and that this may form the basis of cerebellar learning.

Efferents

The Purkinje cells are the only efferent cells of the cerebellum and they project to the cerebellar and vestibular nuclei; they are inhibitory. The fastigial nucleus, the main outflow of the medial cerebellar structures, projects mainly to the vestibular nuclei, brainstem reticular formation, and the spinal cord. The in-

terposed and dentate nuclei relay efferents from more lateral cerebellar structures to the contralateral red nucleus and thalamus via the superior peduncle. These axons also have descending branches to the lower brainstem reticular formation. In the thalamus, cerebellar efferents reach the VL and VPL nuclei which then project to the primary motor cortex (area 4). Thalamic nucleus X also receives cerebellar efferents and projects to the lateral pre-motor cortex (area 6). Although cerebellar projections via the thalamus reach a wide area of cerebral cortex, the bulk of the output is to frontal motor cortex.

Cerebellar function

The cerebellum receives inputs from the cerebral cortex and also from the spinal cord and vestibular system via the mossy and climbing systems, respectively. This may enable a comparison of the motor command and the actual movement of the body, allowing correction and adjustment of the movement. The cerebellum is also involved in the correct planning of movement. Activation of lateral cerebellar cortical neurons occurs before movement, suggesting that cerebellar input to the frontal motor cortex is an important part of preparation for movement. There is evidence that the cerebellum is involved in the correct timing and force of the agonist and antagonist activation during movement; cerebellar dysfunction leads to delayed and prolonged agonist bursts and delayed antagonist activation, leading to dysmetria and dysdiadochokinesis. The cerebellum is also thought to be involved in the learning of motor tasks. There are three main theories of cerebellar function in relation to movement.

A. A feedback control of the ongoing movement. This assumes continuous monitoring of afferent signals from the periphery by the cerebellum. This allows a continuous correction of the motor cortex activity by the cerebellar outflow (feedback mechanism).

B. A centre for the generation of precise motor plans concerning the timing and amplitude of movements which are then sent to the frontal motor cortex for execution (feedforward mechanism).

C. The efference copy theory integrates feedback and feedforward models and assumes that the cerebellum receives a copy of the movement command from the cerebral cortex and compares it to current and ongoing afferent signals from the periphery. The motor command is then adjusted and refined by the cerebellum to allow for the position and motion of the body prior to movement onset and during the execution of the movement itself.

The basal ganglia

The basal ganglia are thought to be important for motor control because of their anatomical connections, the neurophysiological properties of their neurons, and the effects of anatomical lesions and alterations in basal ganglia neurotransmitter function on movement. The basal ganglia are made up of the putamen and

caudate nucleus (neostriatum), the globus pallidus (paleostriatum), the substantia nigra, and the subthalamic nucleus (STN). The inclusion of other nuclear structures such as the nucleus accumbens and parts of the olfactory tubercle (the ventral striatum) has been emphasized recently.

Anatomy and physiology

The putamen, globus pallidus, and caudate nucleus are large masses of grey matter lateral to the thalamus and separated from it by the internal capsule; anteriorly the internal capsule also separates the putamen from the head of the caudate nucleus. The putamen lies lateral to the globus pallidus and these together form the lentiform nucleus with the head of the caudate nucleus lying anteriorly and the body curving over superiorly and then posteriorly in the floor of the lateral ventricle. The subthalamic nucleus and substantia nigra lie inferiorly and caudally in the diencephalon and rostral midbrain, respectively.

The striatum takes its name from the histological appearance caused by efferent myelinated fibres traversing the putamen and caudate. The globus pallidus is subdivided into external (GPe) and internal (GPi) regions which have different connections. The substantia nigra is also divided into a dorsal pars compacta (SNpc) and a ventral pars reticulata (SNpr); the latter is homologous to the GPi.

Connections and functional loops

The striatum is the input region of the basal ganglia and receives excitatory corticostriatal fibres from all areas of the cerebral cortex but mainly the motor and somatosensory areas, prefrontal, and limbic cortex; it also receives the dopaminergic nigrostratal projection. There are two pathways from the striatum to the GPi, the source of the basal ganglia output; a direct pathway and an indirect circuit via Gpe and the STN. The basal ganglia output from GPi (and also SNpr) is inhibitory and is mainly to the thalamus; there is a smaller output to the superior colliculus and the pedunculopontine nucleus. The thalamic output is excitatory and is thought to 'drive' the motor cortical outflow. The input-output connections of the basal ganglia therefore form a loop from cortex to basal ganglia and back to cortex. Several separate and parallel loops through the basal ganglia have been identified (motor, oculomotor, limbic, and prefrontal) depending on the cortical component of the circuit. Different areas of the striatum are involved with different loops; for the motor loop the putamen is the striatal component. Within the striatum there are groups of cells which are more densely packed and contain more substance P, met-enkephalin and opiate receptors but less acetylcholinesterase. These areas 'striosomes' appear to be involved in the processing of the limbic and prefrontal inputs and are seen mainly in the caudate rather than the putamen. The patches also receive most of the dopaminergic afferents from the SNc.

Within the motor loop there are smaller but still separate loops related to different body regions. There is therefore considerable somatotopy within the putamen corresponding to the routes of the various parts of the motor loop. Neurophysiological studies indicate that the various loops remain separate during their course through the basal ganglia although the anatomical studies suggest otherwise.

With regard to the functions of the direct and indirect pathways from putamen to GPi within the motor loop, increased activity in the direct pathway will inhibit basal ganglia outflow and therefore increase motor cortex activation whereas indirect pathway activity increases STN activity and therefore GPi outflow with an opposite effect on motor cortex activity.

The corticostriatal projection is excitatory and glutamatergic and these fibres synapse on the GABA containing medium spiny neurons (MSNs) which are the major cell type in the striatum; the remainder are mainly the large aspiny neurons which are cholinergic and inhibitory to the MSNs. The projection from the putamen to the globus pallidus via the direct or indirect pathways is from the inhibitory MSNs which all utilize GABA; the direct pathway MSNs also contain dynorphin and substance P while the indirect MSNs which project initially to the GPe utilize enkephalin as a co-transmitter. All other circuits within the basal ganglia are inhibitory (utilizing GABA) with the exception of the glutamatergic subthalamic input to the Gpi which is excitatory.

MOTOR DEFICITS

Motor function can be impaired by a lesion that involves the nervous system either centrally or peripherally. Several parts of the central nervous system are involved in the regulation of motor activity; these include the pyramidal and extrapyramidal pathways, the cerebellum, and the lower motor neurons of the brains tern and spinal cord.

The pyramidal system consists of fibers that descend from the cerebral cortex through the internal capsule, traverse the medullary pyramid, and then mostly decussate, to descend in the lateral corticospinal tract on the side opposite that of their origin, where they synapse on lower motor neurons in the spinal cord. All other descending influences on lower motor neurons belong to the extrapyramidal system and originate primarily in the basal ganglia and cerebellum. Disorders of the basal ganglia and cerebellum are considered separately.

The motor fibers that make up the cranial and peripheral nerves have their origin in the lower motor neurons. A disturbance of function at any point in the peripheral nervous system (anterior horn cell, nerve root, limb plexus, peripheral nerve, or neuromuscular junction) can disturb motor function, as can disease that primarily affects the muscles themselves.

Patients with motor deficits generally complain of weakness, heaviness, stiffness, clumsiness, impaired muscular control, or difficulty in executing movements. The term *weakness* is sometimes used in a nonspecific way to denote loss of energy, drive, or enthusiasm, and care must be taken to clarify what the patient means. The word is properly used to mean loss of muscle power, and it is in this sense that it is employed here.

EXAMINATION OF THE MOTOR SYSTEM

In examining the motor system, a systematic approach will help to avoid overlooking important abnormalities. A sequential routine for the examination should be developed.

A. Muscle Appearance. Wasting, or muscle atrophy, suggests that weakness is due to a lesion of the lower motor neurons or of the muscle itself. The distribution of wasting may help to localize the underlying disorder. Upper motor neuron disorders are not usually accompanied by muscle wasting, though muscle atrophy may occasionally occur with prolonged disuse. Pseudohypertrophy of muscles occurs in certain forms of myopathy, but the apparently enlarged muscles are weak and flabby.

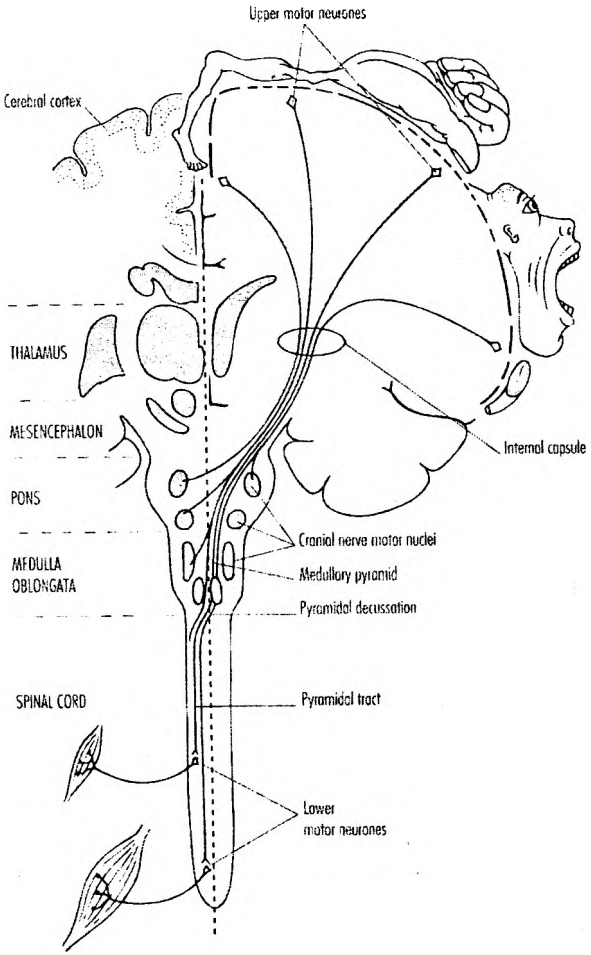

Fig. 1. Schematic representation showing the course of the pyramidal tract, the homuncular organization of the motor cortex in the precentral gyrus, the concentration of the motor output within the internal capsule, and the decussation of the pyramidal tract in the medulla oblongata (from M. Donaghy 1997)

The presence of fasciculations – visible irregular flickerings over the surface of the affected muscle caused by spontaneous contractions of individual motor units – suggests that weakness is due to a lower motor neuron lesion. Fasciculations are most apt to be seen in anterior horn cell disorders. While such activity does not occur with upper motor neuron disorders, flexor or extensor spasms of the limbs are sometimes seen in these latter conditions as a result of impaired supraspinal control of reflex activity.

B. Muscle Tone. For clinical purposes, tone can be defined as the resistance of muscle to passive movement of a joint. Tone depends on the degree of muscle contraction and on the mechanical properties of muscle and connective tissue. The degree of muscle contraction depends, in turn, on the activity of anterior horn cells, which is governed by spinal and supraspinal mechanisms. Tone is assessed by observing the position of the extremities at rest, by palpating the muscle belly, and particularly by determining the resistance to passive stretch and movement. Postural abnormalities may result from the increased activity of certain muscle groups caused by disturbances of reflex function, as exemplified by the typical hemiplegic posture-flexion of the upper limb and extension of the ipsilateral lower limb-of many patients who have had a stroke. To assess resistance to passive movement, the patient is asked to relax while each limb is examined in turn by passively taking the major joints through their full range of movement at different speeds and estimating whether the force required is more or less than normal.

1. Hypertonia. Two types of increased tone can be distinguished.

a. Spasticity. Consists of an increase in tone that affects different muscle groups to different extents. In the arms, tone is increased to a greater extent in the flexor muscles than in the extensors; in the legs, tone is increased to a greater extent in the extensor muscles than in the flexors. Moreover, the resistance of affected muscle is not the same throughout the range of movement but tends to be most marked when passive movement is initiated and then diminishes as the movement continues (the clasp-knife phenomenon). The increase in tone is velocity-dependent, so that passive movement at a high velocity – but not at lower velocities – may be met with increased resistance. Spasticity is caused by an upper motor neuron lesion, such as a stroke that involves the supplementary motor cortex or corticospinal tract. Spasticity may not become apparent for several days following the onset of an acute lesion, however.

b. Rigidity. consists of increased resistance to passive movement that is independent of the direction of the movement – ie, it affects agonist and antagonist muscle groups equally. The term lead-pipe rigidity is sometimes used for descriptive purposes, while cogwheel rigidity is used when there are superimposed ratchetlike interruptions in the passive movement, which probably relate to underlying tremor. In general, rigidity indicates extrapyramidal dysfunction and is due to a lesion of the basal ganglia (eg, Parkinson's disease).

2. Hypotonia (flaccidity). This is characterized by excessive floppiness – a reduced resistance to passive movement – so that the distal portion of the limb is easily waved to and fro when the extremity is passively shaken. In hypotonic limbs it is often possible to hyperextend the joints, and the muscle belly may look flattened and feel less firm than usual. While hypotonia usually relates to pathologic involvement of the lower motor neuron supply to the affected muscles, it can also occur with primary muscle disorders, disruption of the sensory (afferent) limb of the reflex arc, cerebellar disease, and certain extrapyramidal disorders such as Huntington's disease as well as in the acute stage of a pyramidal lesion.

3. Paratonia. Some patients give the impression of being unable to relax and will move the limb being examined as the physician moves it, despite instructions to the contrary. In more advanced cases, there seems to be rigidity when the examiner moves the limb rapidly but normal tone when the limb is moved slowly. This phenomenon – paratonia – is particularly apt to occur in patients with frontal lobe or diffuse cerebral disease.

C. Muscle Power. When muscle power is to be tested, the patient is asked to resist pressure exerted by the examiner. Selected individual muscles are tested in turn, and strength on the two sides is compared so that minor degrees of weakness can be recognized. Weakness can result from a disturbance in function of the upper or the lower motor neurons; the distribution of weakness is of paramount importance in distinguishing between these two possibilities. Upper motor neuron lesions (eg, stroke) lead to weakness that characteristically involves the extensors and abductors more than the flexors and adductors of the arms – and the flexors more than the extensors of the legs. Lower motor neuron lesions produce weakness of the muscles supplied by the affected neurons; the particular distribution of the weakness may point to lower motor neuron involvement at the spinal cord, nerve root, plexus, or peripheral nerve level.

On the basis of the history and other findings, muscles that are particularly likely to be affected are selected for initial evaluation, and other muscles are subsequently examined to determine the distribution of the weakness more fully and to shorten the list of diagnostic possibilities. For instance, if an upper motor neuron (pyramidal) lesion is suspected, the extensors and abductors of the upper extremity and the flexors of the lower extremity are tested in the most detail, since these muscles will be the most affected.

Weakness may also result from a primary muscle disorder (myopathy) or from a disorder of neuromuscular transmission. In patients with a motor deficit in all limbs that is not due to an upper motor neuron lesion, proximal distribution of weakness suggests a myopathic disorder, whereas predominantly distal involvement suggests a lower motor neuron disturbance. Marked variability in the severity and distribution of weakness over short periods of time suggests myasthenia gravis, a disorder of neuromuscular transmission. Apparent weakness that is not organic in nature also shows a characteristic variability; it is of-

ten more severe on formal testing than is consistent with the patient's daily activities. Moreover, palpation of antagonist muscles commonly reveals that they contract each time the patient is asked to activate the agonist.

For practical and comparative purposes, power is best graded in the following manner: 5 – Normal power; 4 – Active movement against resistance and gravity; 3 – Active movement against gravity but not resistance; 2 – Active movement possible only with gravity eliminated; 1 – Flicker or trace of contraction; 0 – No contraction.

Monoplegia denotes paralysis or severe weakness of the muscles in one limb, and monoparesis denotes less severe weakness in one limb, although the two words are often used interchangeably. Hemiplegia or hemiparesis is weakness in both limbs (and sometimes the face) on one side of the body; paraplegia or paraparesis is weakness of both legs; and quadriplegia or quadriparesis (also tetraplegia, tetraparesis) is weakness of all four limbs.

D. Coordination. The coordination of motor activity can be impaired by weakness, sensory disturbances, or cerebellar disease and requires careful evaluation.

Voluntary activity is observed with regard to its accuracy, velocity, range, and regularity, and the manner in which individual actions are integrated to produce a smooth complex movement. In the fingernose test, the patient moves the index finger to touch the tip of his or her nose and then the tip of the examiner's index finger; the examiner can move his or her own finger about during the test to change the location of the target and should position it so that the patient's arm must extend fully to reach it. In the heel-knee-shin test, the recumbent patient lifts one leg off the bed, flexes it at the knee, places the heel on the other knee, and runs the heel down the shin as smoothly as possible.

The patient should also be asked to tap repetitively with one hand on the back of the other; to tap alternately with the palm and back of one hand on the back of the other hand or on the knee; to screw an imaginary light bulb into the ceiling with each arm in turn; and to rub the fingers of one hand in a circular polishing movement on the back of the other hand. Other tests of rapid alternating movement include tapping on the ball of the thumb with the tip of the index finger or tapping the floor as rapidly as possible with the sole while keeping the heel of the foot in place. During all these tests, the examiner looks for irregularities of rate, amplitude, and rhythm and for precision of movements. With pyramidal lesions, fine voluntary movements are performed slowly. With cerebellar lesions, the rate, rhythm, and amplitude of such movements are irregular.

If loss of sensation may be responsible for impaired coordination, the maneuver should be repeated both with eyes closed and with visual attention directed to the limb; with visual feedback the apparent weakness or incoordination will improve. In patients with cerebellar disease, the main complaint and physical finding are often of incoordination, and examination may reveal little else.

E. Tendon Reflexes. Changes in the tendon reflexes may accompany disturbances in motor (or sensory) function and provide a guide to the cause of the motor deficit. The tendon is tapped with a reflex hammer to produce a sudden brisk stretch of the muscle and its contained spindles. When the reflexes are tested, the limbs on each side should be placed in identical positions and the reflexes elicited in the same manner.

1. Areflexia. Apparent loss of the tendon reflexes in a patient may merely reflect a lack of clinical expertise on the part of the examiner. Performance of Jendrassik's maneuver (an attempt by the patient to pull apart the fingers of the two hands when they are hooked together) or some similar action (such as making a fist with the hand that is not being tested) may elicit the reflex response when it is otherwise unobtainable. A reflex may be lost or depressed by any lesion that interrupts the structural or functional continuity of its reflex arc, as in a root lesion or peripheral neuropathy. In addition, reflexes are often depressed during the acute stage of an upper motor neuron lesion, in patients who are deeply comatose, and in patients with cerebellar disease.

2. Hyperreflexia. Increased reflexes occur with upper motor neuron lesions, but they may also occur with symmetric distribution in certain healthy subjects and in patients under emotional tension. The presence of reflex asymmetry is therefore of particular clinical significance. Clonus consists of a series of rhythmic reflex contractions of a muscle that is suddenly subjected to sustained stretch, with each beat caused by renewed stretch of the muscle during relaxation from its previous contracted state. Sustained clonus – more than three or four beats in response to sudden sustained stretch – is always pathologic and is associated with an abnormally brisk reflex. In hyperreflexic states, there may be spread of the region from which a particular reflex response can be elicited. For example, elicitation of the biceps reflex may be accompanied by reflex finger flexion, or eliciting the finger flex ion reflex may cause flexion of the thumb (Hoffmann's sign).

3. Reflex asymmetry. Although the intensity of reflex responses varies considerably among subjects, reflexes should be symmetric in any individual. Several general points can be made regarding reflex asymmetries.

a. Lateralized asymmetries of response – ie, reflexes that are brisker on one side of the body than on the other – usually indicate an upper motor neuron disturbance.

b. Focal reflex deficits often relate to root, plexus, or peripheral nerve lesions. For example, unilateral depression of the ankle jerk commonly reflects an SI radiculopathy resulting from a lumbosacral disk lesion.

c. Loss of distal tendon reflexes (especially ankle jerks), with preservation of more proximal ones, is common in polyneuropathies.

F. Superficial Reflexes

1. The polysynaptic superficial abdominal reflexes, which depend on the integrity of the T8-12 spinal cord segments, are elicited by gently stroking

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each quadrant of the abdominal wall with a blunt object such as a wooden stick. A normal response consists of contraction of the muscle in the quadrant stimulated, with a brief movement of the umbilicus toward the stimulus. Asymmetric loss of the response may be of diagnostic significance.

a. The response may be depressed or lost on one side in patients with an upper motor neuron disturbance from a lesion of the contralateral motor cortex or its descending pathways.

b. Segmental loss of the response may relate to local disease of the abdominal wall or its innervation, as in a radiculopathy.

c. The cutaneous abdominal reflexes are frequently absent bilaterally in the elderly, in the obese, in multiparous women, and in patients who have had abdominal surgery.

2. The cremasteric reflex, mediated through the L1 and L2 reflex arcs, consists of retraction of the ipsilateral testis when the inner aspect of the thigh is lightly stroked; it is lost in patients with a lesion involving these nerve roots. It is also lost in patients with contralateral upper motor neuron disturbances.

3. Stimulation of the lateral border of the foot in a normal adult leads to plantar flexion of the toes and dorsiflexion of the ankle. The Babinski response consists of dorsiflexion of the big toe and fanning of the other toes in response to stroking the lateral border of the foot, which is part of the S1 dermatome; flexion at the hip and knee may also occur. Such an extensor plantar response indicates an upper motor neuron lesion involving the contralateral motor cortex or the corticospinal tract. It can also be found in anesthetized or comatose subjects, in patients who have had a seizure, and in normal infants. An extensor plantar response can also be elicited, though less reliably, by such maneuvers as pricking the dorsal surface of the big toe with a pin (Bing's sign), firmly stroking down the anterior border of the tibia from knee to ankle (Oppenheim's maneuver), squeezing the calf muscle (Gordon's maneuver) or Achilles tendon (Schafer's maneuver), flicking the little toe (Gonda's maneuver), or stroking the back of the foot just below the lateral malleolus (Chaddock's maneuver). In interpreting responses, attention must be focused only on the direction in which the big toe first moves.

G. Gait. In evaluating gait, the examiner first observes the patient walking at a comfortable pace. Attention is directed at the stance and posture; the facility with which the patient starts and stops walking and turns to either side; the length of the stride; the rhythm of walking; the presence of normally associated movements, such as swinging of the arms; and any involuntary movements. Subtle gait disorders become apparent only when the patient is asked to run, walk on the balls of the feet or the heels, hop on either foot, or walk heel-to-toe along a straight line. Gait disorders occur in many neurologic disturbances and in other contexts that are beyond the scope of this chapter. A motor or sensory disturbance may lead to an abnormal gait whose nature depends upon the site of

pathologic involvement. Accordingly, the causes and clinical types of gait disturbance are best considered together.

1. Apraxic gait. Apraxic gait occurs in some patients with disturbances, usually bilateral, of frontal lobe function, such as may occur in hydrocephalus or progressive dementing disorders. There is no weakness or incoordination of the limbs, but the patient is unable to stand unsupported or to walk properly – the feet seem glued to the ground. If walking is possible at all, the gait is unsteady, uncertain, and short-stepped, with marked hesitation ("freezing"), and the legs are moved in a direction inappropriate to the center of gravity.

2. Corticospinal lesions. A corticospinal lesion, irrespective of its cause, can lead to a gait disturbance that varies in character depending on whether there is unilateral or bilateral involvement. In patients with hemiparesis, the selective weakness and spasticity lead to a gait in which the affected leg must be circumducted to be advanced. The patient tilts at the waist toward the normal side and swings the affected leg outward as well as forward, thus compensating for any tendency to drag or catch the foot on the ground because of weakness in the hip and knee flexors or the ankle dorsiflexors. The arm on the affected side is usually held flexed and adducted. In mild cases, there may be no more than a tendency to drag the affected leg, so that the sole of that shoe tends to be excessively worn.

With severe bilateral spasticity, the legs are brought stiffly forward and adducted, often with compensatory movements of the trunk. Such a gait is commonly described as scissorslike. This gait is seen in its most extreme form in children with spastic diplegia from perinatally acquired static encephalopathy. In patients with mild spastic paraparesis, the gait is shuffling, slow, stiff, and awkward, with the feet tending to drag.

3. Frontal disorders. Some patients with frontal lobe or white matter lesions have a gait characterized by short, shuffling steps; hesitation in starting or turning; unsteadiness; and a wide or narrow base. Sometimes referred to as *marche a petit pas*, this abnormality may be mistaken for a parkinsonian gait, but the wide base, preserved arm swing, absence of other signs of parkinsonism, and accompanying findings of cognitive impairment, frontal release signs, pseudobulbar palsy, pyramidal deficits, and sphincter disturbances are helpful in indicating the correct diagnosis.

4. Extrapyramidal disorders. Extrapyramidal disorders can produce characteristic gait disturbances.

a. In advanced parkinsonism, the patient is often stooped and has difficulty in beginning to walk. Indeed, the patient may need to lean farther and farther forward while walking in place in order to advance; once in motion, there may be unsteadiness in turning and difficulty in stopping. The gait itself is characterized by small strides, often taken at an increasing rate until the patient is almost running (festination), and by loss of the arm swinging that normally ac-

companies locomotion. In mild parkinsonism, a mildly slowed or unsteady gait, flexed posture, or reduced arm swinging may be the only abnormality found.

b. Abnormal posturing of the limbs or trunk is a feature of dystonia; it can interfere with locomotion or lead to a distorted and bizarre gait.

c. Chorea can cause an irregular, unpredictable, and unsteady gait, as the patient dips or lurches from side to side. Choreiform movements of the face and extremities are usually well in evidence.

d. Tremor that occurs primarily on standing (orthostatic tremor) may lead to an unsteady, uncertain gait, with hesitancy in commencing to walk.

5. Cerebellar disorders. In cerebellar disorders the gait may be disturbed in several ways.

a. Truncal ataxia results from involvement of midline cerebellar structures, especially the vermis. The gait is irregular, clumsy, unsteady, uncertain, and broad-based, with the patient walking with the feet wide apart for additional support. Turning and heel-to-toe walking are especially difficult. There are often few accompanying signs of a cerebellar disturbance in the limbs. Causes include midline cerebellar tumors and the cerebellar degeneration that can occur with alcoholism or hypothyroidism, as a nonmetastatic complication of cancer, and with certain hereditary disorders.

b. In extreme cases, with gross involvement of midline cerebellar structures (especially the vermis), the patient cannot stand without falling.

c. A lesion of one cerebellar hemisphere leads to an unsteady gait in which the patient consistently falls or lurches toward the affected side.

6. Impaired sensation. Impaired sensation, especially disturbed proprioception, also leads to an unsteady gait, which is aggravated by walking in the dark or with the eyes closed, since visual input can not then compensate for the sensory loss. Because of their defective position sense, many patients lift their feet higher than necessary when walking, producing a steppage gait. Causes include tabes dorsalis, sensory neuropathies, vitamin B_{12} deficiency, and certain hereditary disorders.

7. Anterior horn cell, peripheral motor nerve, or voluntary muscle disorders. These disorders lead to gait disturbances if the muscles involved in locomotion are affected. Weakness of the anterior tibial muscles leads to foot drop; to avoid catching or scuffing the foot on the ground, the patient must lift the affected leg higher than the other, in a characteristic steppage gait. Weakness of the calf muscles leads to an inability to walk on the balls of the feet. Weakness of the trunk and girdle muscles, such as occurs in muscular dystrophy, other myopathic disorders, and Kugelberg-Welander syndrome, leads to a waddling gait because the pelvis tends to slump toward the non-weight-bearing side.

8. Unsteady gait in the elderly. Many elderly persons complain of unsteadiness when walking and a fear of falling, but neurologic examination reveals no abnormality. Their symptoms have been attributed to reduced sensory

input from several different afferent systems and impaired central processing of sensory input; an impairment of vestibular function may also be important.

CLINICAL LOCALIZATION OF THE LESION

The findings on examination should indicate whether the weakness or other motor deficit is due to an upper or lower motor neuron disturbance, a disorder of neuromuscular transmission, or a primary muscle disorder. In the case of an upper or lower motor neuron disturbance, the clinical findings may also help to localize the lesion more precisely to a single level of the nervous system. Such localization helps to reduce the number of diagnostic possibilities.

Upper Motor Neuron Lesions

A. Signs:

- Weakness or paralysis
- Spasticity
- Increased tendon reflexes
- An extensor plantar (Babinski) response
- Loss of superficial abdominal reflexes
- Little, if any, muscle atrophy

Such signs occur with involvement of the upper motor neuron at any point, but further clinical findings depend upon the actual site of the lesion. Note that it may not be possible to localize a lesion by its motor signs alone.

B. Localization of Underlying Lesion:

1. A parasagittal intracranial lesion produces an upper motor neuron deficit that characteristically affects both legs and may later involve the arms.

2. A discrete lesion of the cerebral cortex or its projections may produce a focal motor deficit involving, for example, the contralateral hand. Weakness may be restricted to the contralateral leg in patients with anterior cerebral artery occlusion or to the contralateral face and arm if the middle cerebral artery is involved. A more extensive cortical or subcortical lesion will produce weakness or paralysis of the contralateral face, arm, and leg and may be accompanied by aphasia, a visual field defect, or a sensory disturbance of cortical type.

3. A lesion at the level of the internal capsule, where the descending fibers from the cerebral cortex are closely packed, commonly results in a severe hemiparesis that involves the contralateral limbs and face.

4. A brainstem lesion commonly – but not invariably – leads to bilateral motor deficits, often with accompanying sensory and cranial nerve disturbances, and disequilibrium. A more limited lesion involving the brainstem characteristically leads to a cranial nerve disturbance on the ipsilateral side and a contralateral hemiparesis; the cranial nerves affected depend on the level at which the brainstem is involved.

5. A unilateral spinal cord lesion above the fifth cervical segment (C5) causes an ipsilateral hemiparesis that spares the face and cranial nerves. Lesions between C5 and the first thoracic segment (T1) affect the ipsilateral arm to a variable extent as well as the ipsilateral leg; a lesion below T1 will affect only the ipsilateral leg. Because, in practice, both sides of the cord are commonly involved, quadriparesis or paraparesis usually results. If there is an extensive but unilateral cord lesion, the motor deficit is accompanied by ipsilateral impairment of vibration and position sense and by contralateral loss of pain and temperature appreciation (Brown-Sequard syndrome). With compressive and other focal lesions that involve the anterior horn cells in addition to the fiber tracts traversing the cord, the muscles innervated by the affected cord segment weaken and atrophy. Therefore, a focal lower motor neuron deficit exists at the level of the lesion and an upper motor neuron deficit exists below it – in addition to any associated sensory disturbance.

Lower Motor Neuron Lesions

A. Signs:

- Weakness or paralysis
- Wasting and fasciculations of involved muscles
- Hypotonia (flaccidity)
- Loss of tendon reflexes when neurons subserving them are affected
- Normal abdominal and plantar reflexes – unless the neurons subserving them are directly involved, in which case reflex responses are lost

B. Localization of the Underlying Lesion. In distinguishing weakness from a root, plexus, or peripheral nerve lesion, the distribution of the motor deficit is of particular importance. Only those muscles supplied wholly or partly by the involved structure are weak. The distribution of any accompanying sensory deficit similarly reflects the location of the underlying lesion. It may be impossible to distinguish a radicular (root) lesion from discrete focal involvement of the spinal cord. In the latter situation, however, there is more often a bilateral motor deficit at the level of the lesion, a corticospinal or sensory deficit below it, or a disturbance of bladder, bowel, or sexual function. Certain disorders selectively affect the anterior horn cells of the spinal cord diffusely or the motor

nerves; the extensive lower motor neuron deficit without sensory changes helps to indicate the site and nature of the pathologic involvement.

Cerebellar Dysfunction

A. Signs:

- Hypotonia
- Depressed or pendular tendon reflexes
- Ataxia
- Gait disorder
- Imbalance of station
- Disturbances of eye movement
- Dysarthria

Ataxia is a complex movement disorder caused, at least in part, by impaired coordination. It occurs in the limbs on the same side as a lesion affecting the cerebellar hemisphere. With midline lesions, incoordination may not be evident in the limbs at all, but there is marked truncal ataxia that becomes evident on walking. The term dysmetria is used when movements are not adjusted accurately for range, so that for example – a moving finger overshoots a target at which it is aimed. Dysdiadochokinesia denotes rapid alternating movements that are clumsy and irregular in terms of rhythm and amplitude. Asynergia or dyssynergia denotes the breakdown of complex actions into the individual movements composing them; when asked to touch the tip of the nose with a finger, for example, the patient may first flex the elbow and then bring the hand up to the nose instead of combining the maneuvers into one action. Intention tremor occurs during activity and is often most marked as the target is neared. The rebound phenomenon is the overshooting of the limb when resistance to a movement or posture is suddenly withdrawn.

The gait becomes unsteady in patients with disturbances of either the cerebellar hemispheres or midline structures.

Jerk nystagmus, which is commonly seen in patients with a unilateral lesion of the cerebellar hemisphere, is slowest and of greatest amplitude when the eyes are turned to the side of the lesion. Nystagmus is not present in patients with lesions of the anterior cerebellar vermis.

Speech becomes dysarthric and takes on an irregular and explosive quality in patients with lesions that involve the cerebellar hemispheres. Speech is usually unremarkable when only the midline structures are involved.

B. Localization of the Underlying Lesion. The relationship of symptoms and signs to lesions of different parts of the cerebellum is considered later.

Neuromuscular-Transmission Disorders

A. Signs:

- Normal or reduced muscle tone
- Normal or depressed tendon and superficial reflexes
- No sensory changes
- Weakness, often patchy in distribution, not conforming to the distribution of any single anatomic structure; frequently involves the cranial muscles and may fluctuate in severity over short periods, particularly in relation to activity

B. Localization of the Underlying Lesion. Pathologic involvement of either the pre- or postsynaptic portion of the neuromuscular junction may impair neuromuscular transmission. Disorders affecting neuromuscular transmission are discussed below.

Myopathic Disorders

A. Signs:

- Weakness, usually most marked proximally rather than distally
- No muscle wasting or depression of tendon reflexes until at least an advanced stage of the disorder
- Normal abdominal and plantar reflexes
- No sensory loss or sphincter disturbances

B. Differentiation. In distinguishing the various myopathic disorders, it is important to determine whether the weakness is congenital or acquired, whether there is a family history of a similar disorder, and whether there is any clinical evidence that a systemic disease may be responsible. The distribution of affected muscles is often especially important in distinguishing the various hereditary myopathies.

MOVEMENT (EXTRAPYRAMIDAL) DISORDERS

Movement disorders (sometimes called extrapyramidal disorders) impair the regulation of voluntary motor activity without directly affecting strength, sensation, or cerebellar function. They include hyperkinetic disorders associated with abnormal, involuntary movements and hypokinetic disorders characterized by poverty of movement. Movement disorders result from dysfunction of deep subcortical gray matter structures termed the basal ganglia. While there is no universally accepted anatomic definition of the basal ganglia, for clinical purposes they may be considered to comprise the caudate nucleus, putamen, globus pallidus, subthalamic nucleus, and substantia nigra. The putamen and globus pallidus are collectively termed the lentiform nucleus; the combination of lentiform nucleus and caudate nucleus is designated the corpus striatum.

The basic circuitry of the basal ganglia consists of three interacting neuronal loops. The first is a corticocortical loop that passes from the cerebral cortex, through the caudate and putamen, the internal segment of globus pallidus, and the thalamus, and then back to the cerebral cortex. The second is a nigrostriatal loop connecting the substantia nigra with the caudate and putamen. The third, a striatopallidal loop, projects from the caudate and putamen to the external segment of globus pallidus, then to the subthalamic nucleus, and finally to the internal segment of globus pallidus. In some movement disorders (eg, Parkinson's disease), a discrete site of pathology within these pathways can be identified; in other cases (eg, essential tremor), the precise anatomic abnormality is unknown.

TYPES OF ABNORMAL MOVEMENTS

Categorizing an abnormal movement is generally the first step toward arriving at the neurologic diagnosis. Abnormal movements can be classified as tremor, chorea, athetosis or dystonia, ballismus, myoclonus, or tics. Such movements can arise for a variety of reasons. In many disorders, abnormal movements are the sole clinical features.

TREMOR

A tremor is a rhythmic oscillatory movement best characterized by its relationship to voluntary motor activity – ie, according to whether it occurs at rest, during maintenance of a particular posture, or during movement. The major causes of tremor are listed below. Tremor is enhanced by emotional stress and

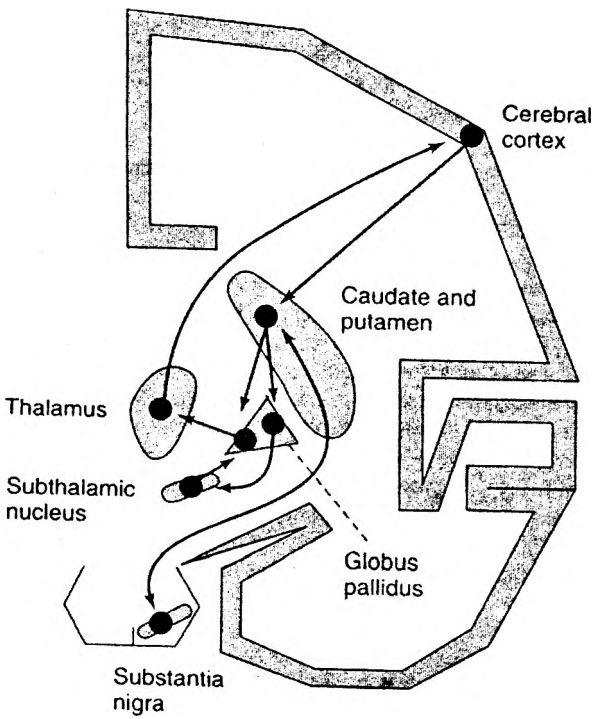


Fig. 2. Basic neuronal circuity of the basal ganglia (From R. Simon, M. Aminoff, D. Greenberg, 1999)

disappears during sleep. Tremor that occurs when the limb is at rest is generally referred to as static tremor or rest tremor. If present during sustained posture, it is called a postural tremor; while this tremor may continue during movement, movement does not increase its severity. When present during movement but not at rest, it is generally called an intention tremor. Both postural and intention tremors are also called action tremors.

Postural Tremor

A. Physiologic Tremor. An 8- to 12-Hz tremor of the outstretched hands is a normal finding. Its physiologic basis is uncertain.

B. Enhanced Physiologic Tremor. Physiologic tremor may be enhanced by fear or anxiety. A more conspicuous postural tremor may also be found following excessive physical activity or sleep deprivation. It can complicate treatment with certain drugs (notably lithium, tricyclic antidepressants, sodium valproate, and bronchodilators) and is often conspicuous in patients with alcoholism or in alcohol or drug withdrawal states. It is common in thyrotoxicosis, and it can also result from poisoning with a number of substances, including mercury, lead, arsenic, and carbon monoxide. There is no specific medical therapy.

C. Other Causes. The most common type of abnormal postural tremor is benign essential trem or, which often has a familial basis. Postural tremor may also be conspicuous in patients with Wilson's disease or cerebellar disorders.

Causes of tremor

Postural tremor

Physiologic tremor

Enhanced physiologic tremor

Anxiety or fear

Excessive physical activity or sleep deprivation Sedative drug or alcohol withdrawal

Drug toxicity (eg, lithium, bronchodilators, sodium valproate, tricyclic antidepressants)

Heavy metal poisoning (eg, mercury, lead, arsenic) Carbon monoxide poisoning

Thyrotoxicosis

Familial (autosomal dominant) or idiopathic (benign essential) tremor

Cerebellar disorders

Wilson's disease

Intention tremor

Brainstem or cerebellar disease

Drug toxicity (eg, alcohol, anticonvulsants, sedatives)

Wilson's disease

Rest tremor

Parkinsonism
Wilson's disease
Heavy metal poisoning (eg, mercury)

Asterixis

Asterixis may be associated with postural tremor, but is itself more properly considered a form of myoclonus (see below) than of tremor. It is seen most commonly in patients with metabolic encephalopathy such as occurs with hepatic or renal failure.

To detect asterixis, the examiner asks the patient to hold the arms outstretched with fingers and wrists extended. Episodic cessation of muscular activity causes sudden flex ion at the wrists followed by a return to extension, so that the hands flap in a regular or, more often, an irregular rhythm. The asterixis resolves with clearing of the metabolic encephalopathy.

Intention Tremor

Intention tremor occurs during activity. If the patient is asked to touch his or her nose with a finger, for example, the arm exhibits tremor during movement, often more marked as the target is reached. This form of tremor is sometimes mistaken for limb ataxia, but the latter has no rhythmic oscillatory component.

Intention tremor results from a lesion affecting the superior cerebellar peduncle. Because it is often very coarse, it can lead to severe functional disability. No satisfactory medical treatment exists, but stereotactic surgery of the ventrolateral nucleus of the thalamus is sometimes helpful when patients are severely incapacitated.

Intention tremor can also occur-together with other signs of cerebellar involvement-as a manifestation of toxicity of certain sedative or anticonvulsant drugs (such as phenytoin) or alcohol; it is seen in patients with Wilson's disease.

Rest Tremor

A. Parkinsonism. Rest tremor usually has a frequency of 4-6 Hz and is characteristic of parkinsonism whether the disorder is idiopathic or secondary (ie, postencephalitic, toxic, or drug-induced in origin). The rate of the tremor, its relationship to activity, and the presence of rigidity or hypokinesia usually distinguish the tremor of parkinsonism from other forms. Tremor in the hands may appear as a "pill-rolling" maneuver-rhythmic, opposing circular movements of the thumb and index finger. There may be alternating flexion and extension of the fingers or hand, or alternating pronation and supination of the forearm; in the feet, rhythmic alternating flexion and extension are common. Parkinsonism is discussed in more detail later.

B. Other Causes. Less common causes of rest tremor include Wilson's disease and poisoning with heavy metals such as mercury.

CHOREA

The word chorea denotes rapid irregular muscle jerks that occur involuntarily and unpredictably in different parts of the body. In florid cases, the often forceful involuntary movements of the limbs and head and the accompanying facial grimacing and tongue movements are unmistakable. Voluntary movements may be distorted by the superimposed involuntary ones. In mild cases, however, patients may exhibit no more than a persistent restlessness and clumsiness. Power is generally full, but there may be difficulty in maintaining muscular contraction such that, for example, hand grip is relaxed intermittently (milkmaid grasp). The gait becomes irregular and unsteady, with the patient suddenly dipping or lurching to one side or the other (dancing gait). Speech often becomes irregular in volume and tempo and may be explosive in character. In some patients, athetotic movements or dystonic posturing may also be prominent. Chorea disappears during sleep.

Classification & Pathology

The pathologic basis of chorea is unclear, but in some cases it is associated with cell loss in the caudate nucleus and putamen, and it can be provoked by dopaminergic agonist drugs. The important causes of chorea are shown in Table 8-2 and are discussed later in this chapter. When chorea is due to a treatable medical disorder, such as polycythemia vera or thyrotoxicosis, adequate treatment of the primary disorder abolishes the dyskinesia.

Causes of chorea

Hereditary
- Huntington's disease
- Benign hereditary chorea
- Wilson's disease
- Paroxysmal choreoathetosis
- Familial chorea with associated acanthocytosis

Static encephalopathy (cerebral palsy) acquired antenatally or perinatally (eg, from anoxia, hemorrhage, trauma, kernicterus)

Sydenham's chorea

Chorea gravidarum

Drug toxicity
- Levodopa and other dopaminergic drugs Antipsychotic drugs
- Lithium
- Phenytoin
- Oral contraceptives

Miscellaneous medical disorders

Thyrotoxicosis, hypoparathyroidism, or Addison's disease
Hypocalcemia, hypomagnesemia, or hypernatremia Polycythemia vera
Hepatic cirrhosis
Systemic lupus erythematosus
Encephalitis lethargica
Cerebrovascular disorders
Vasculitis
Ischemic or hemorrhagic stroke
Subdural hematoma

Structural lesions of the subthalamic nucleus

HEMIBALLISMUS

Hemiballismus is unilateral chorea that is especially violent because the proximal muscles of the limbs are involved. It is due most often to vascular disease in the contralateral subthalamic nucleus and commonly resolves spontaneously in the weeks following its onset. It is sometimes due to other types of structural disease; in the past, it was an occasional complication of thalamotomy. Pharmacologic treatment is similar to that for chorea.

DYSTONIA & ATHETOSIS

The term athetosis generally denotes abnormal movements that are slow, sinuous, and writhing in character. When the movements are so sustained that they are better regarded as abnormal postures, the term dystonia is used, and many now use the terms interchangeably. The abnormal movements and postures may be generalized or restricted in distribution. In the latter circumstance, one or more of the limbs may be affected (segmental dystonia) or the disturbance may be restricted to localized muscle groups (focal dystonia).

The abnormal movements are not present during sleep. They are generally enhanced by emotional stress and by voluntary activity. In some cases, abnonnal movements or postures occur only during voluntary activity and sometimes only during specific activities such as writing, speaking, or chewing.

Etiology

Perinatal anoxia, birth trauma, and kernicterus are the most common causes. In these circumstances, abnonnal movements usually develop before age 5 years. Careful questioning usually discloses a history of abnonnal early development and often of seizures. Examination may reveal signs of mental retardation or a pyramidal deficit in addition to the movement disorder.

Torsion dystonia may occur as a manifestation of Wilson's disease or Huntington's disease or as a sequela of previous encephalitis lethargica. Dystonic movements and postures are the cardinal features of the disorder

known as idiopathic torsion dystonia. Acute dystonic posturing may result from treatment with dopamine receptor antagonist drugs. Lateralized dystonia may occasionally relate to focal intracranial disease, but the clinical context in which it occurs usually identifies the underlying cause.

Causes of dystonia and athetosis

Static perinatal encephalopathy (cerebral palsy)
Pelizaeus-Merzbacher disease
Neuroacanthocytosis
Wilson's disease
Huntington's disease
Parkinson's disease
Drugs
    Levodopa
    Antipsychotic drugs
    Others (see text)
Toxins (eg, methanol, manganese) Encephalitis lethargica
Ischemic anoxia
Focal intracranial disease
Progressive supranuclear palsy
Idiopathic torsion dystonia
    Hereditary
    Sporadic
Formes frustes of idiopathic torsion dystonia
Dopa-responsive dystonia
Myoclonic dystonia
Psychogenic

MYOCLONUS

Myoclonic jerks are sudden, rapid, twitchlike muscle contractions. They can be classified according to their distribution, relationship to precipitating stimuli, or etiology. Generalized myoclonus has a widespread distribution, while focal or segmental myoclonus is restricted to a particular part of the body. Myoclonus can be spontaneous, or it can be brought on by sensory stimulation, arousal, or the initiation of movement (action myoclonus). Myoclonus may occur as a normal phenomenon (physiologic myoclonus) in healthy persons, as an isolated abnonnality (essential myoclonus), or as a manifestation of epilepsy (epileptic myoclonus). It can also occur as a feature of a variety of degenerative, infectious, and metabolic disorders (symptomatic myoclonus).

Generalized Myoclonus

Physiologic myoclonus includes the myoclonus that occurs upon falling asleep or awakening (nocturnal myoclonus), as well as hiccup. Essential myoclonus is a benign condition that occurs in the absence of other neurologic abnonnalities and is sometimes inherited. Epileptic myoclonus may be impossible to differentiate clinically from nonepileptic fonns. It may be possible to distinguish the two types electrophysiologically, however, by the duration of the electromyographic burst associated with the jerking, by demonstrating an EEG correlate with a consistent temporal relationship to the jerks, or by determining whether muscles involved in the same jerk are activated synchronously.

Causes of generalized myoclonus

Physlologlc myoclonus
- Nocturnal myoclonus
- Hiccup

Essential myoclonus

Epileptic myoclonus

Symptomatic myoclonus
- Degenerative disorders
  - Dentatorubrothalamic atrophy (Ramsay Hunt syndrome) Storage diseases (eg, Lafora body disease)
  - Wilson's disease
  - Huntington's disease
  - Myoclonic dystonia
  - Alzheimer's disease
- Infectious disorders
  - Creutzfeldt-Jakob disease
  - AIDS dementia complex
  - Subacute sclerosing panencephalitis
  - Encephalitis lethargica
  - Viral encephalitis

Metabolic disorders
- Drug intoxications (eg, penicillin, antidepressants, bismuth, levodopa, anticonvulsants)
- Drug withdrawal (ethanol, sedatives)
- Hypoglycemia
- Hyperosmolar nonketotic hyperglycemia
- Hyponatremia
- Hepatic encephalopathy
- Uremia
- Hypoxia
- Focal brain damage

Head injury
Stroke
Tumors

Segmental Myoclonus

Segmental myoclonus can arise from lesions affecting the cerebral cortex, brainstem, or spinal cord. For example, involvement of the dentatorubro-olivary pathway by stroke, multiple sclerosis, tumors, or other disorders can produce palatal myoclonus, which may be associated with an audible click or synchronous movements of ocular, facial, or other bulbar muscles. Segmental myoclonus can result from many of the same disturbances that produce symptomatic generalized myoclonus. Metabolic disorders such as hyperosmolar nonketotic hyperglycemia can cause epilepsia partialis continua, in which a repetitive focal epileptic discharge occurs from the contralateral sensorimotor cortex and leads to segmental myoclonus. Segmental myoclonus is usually unaffected by external stimuli and persists during sleep.

Treatment

Although myoclonus can be difficult to treat, it sometimes responds to anticonvulsant drugs such as valproic acid, 250-500 mg orally three times daily, or to benzodiazepines such as clonazepam, 0.5 mg orally three times daily, gradually increased to as much as 12 mg/d. Postanoxic action myoclonus has been found to be remarkably responsive to 5-hydroxytryptophan, the metabolic precursor of the neurotransmitter 5-hydroxytryptamine (serotonin). The dosage of 5-hydroxytryptophan is increased gradually to a maximum of 1-1.5 mg/d orally and may be combined with carbidopa (maximum, 400 mg/d orally) to inhibit metabolism in peripheral tissues.

TICS

Tics are sudden, recurrent, quick, coordinated abnormal movements that can usually be imitated without difficulty. The same movement occurs again and again and can be suppressed voluntarily for short periods, although doing so may cause anxiety. Tics tend to worsen with stress, diminish during voluntary activity or mental concentration, and disappear during sleep.

Tics can be classified into four groups depending upon whether they are simple or multiple and transient or chronic. Transient simple tics are very common in children, usually terminate spontaneously within 1 year (often within a few weeks), and generally require no treatment. Chronic simple tics can develop at any age but often begin in childhood, and treatment is unnecessary in most cases. The benign nature of the disorder must be explained to the patient.

Persistent simple or multiple tics of childhood or adolescence generally begin before age 15 years. There may be single or multiple motor tics-and often vocal tics-but complete remission occurs by the end of adolescence.

The syndrome of chronic multiple motor and vocal tics is generally referred to as Gilles de la Tourette's syndrome, after the French physician who was one of the first to describe its clinical features. It is discussed in detail later.

EXAMINATION

Clinical examination will indicate the nature of the abnormal movements, the extent of neurologic involvement, and the presence of coexisting disease; these in turn may suggest the diagnosis.

The mental status examination may suggest psychiatric disease, raising the possibility that the abnormal movements are related to the psychiatric disorder or to its treatment with psychoactive drugs-or that the patient has a disorder characterized by both abnormal movements and behavioral disturbances, such as Huntington's disease or Wilson's disease.

Focal motor or sensory deficits raise the possibility of a structural space-occupying lesion, as does papilledema. Kayser-Fleischer rings suggest Wilson's disease. Signs of vascular, hepatic, or metabolic disease may suggest other causes for a movement disorder, such as acquired hepatocerebral degeneration or vasculitis.

Serum and urine copper and serum ceruloplasmin levels are important in diagnosing Wilson's disease. Complete blood count and sedimentation rate are helpful in excluding polycythemia, vasculitis, or systemic lupus erythematosus, any of which can occasionally lead to a movement disorder. Blood chemistries may reveal hepatic dysfunction related to Wilson's disease or acquired hepatocerebral degeneration; hyperthyroidism or hypocalcemia as a cause of chorea; or a variety of metabolic disorders associated with myoclonus.

Serologic tests are helpful for diagnosing movement disorders caused by systemic lupus erythematosus. Neurosyphilis can be manifested clinically in a variety of ways and should always be excluded by appropriate serologic tests in patients with neurologic disease of uncertain etiology.

An EEG is sometimes helpful in diagnosing patients with myoclonus; otherwise, it is of limited usefulness.

Radiologic studies are occasionally helpful in evaluating patients with movement disorders. In some patients, intracranial calcification may be found by skull x-rays or er scans; the significance of this finding, however, is not clear. CT scans or MRI may also reveal a tumor associated with focal dyskinesia or dystonia, caudate atrophy due to Huntington's disease, or basal ganglia abnormalities associated with Wilson's disease.

Recombinant DNA technology has been used to generate probes for genes that determine certain inheritable movement disorders. In this manner, the gene responsible for Huntington's disease has been localized to the terminal band of the short arm of chromosome 4, and the gene for Wilson's disease to the long arm of chromosome 13. Genetic markers are therefore of diagnostic value in such disorders. Their use may be limited, however, by the genetic heterogeneity of some diseases, imprecise gene localization by certain probes, ethical concerns about adverse psychological reactions to the presymptomatic diagnosis of fatal disorders, and the potential for misuse of such information by prospective employers, insurance companies, and government agencies.

ATAXIA

Ataxia is incoordination or clumsiness of movement that is not the result of muscular weakness. It is caused by vestibular, cerebellar, or sensory (proprioceptive) disorders. Ataxia can affect eye movement, speech (producing dysarthria), individual limbs, the trunk, stance, or gait.

Cerebellar Ataxia

Cerebellar ataxia is produced by lesions of the cerebellum itself or its afferent or efferent connections in the cerebellar peduncles, red nucleus, pons, or spinal cord. Because of the crossed connection between the frontal cerebral cortex and the cerebellum, unilateral frontal disease can also occasionally mimic a disorder of the contralateral cerebellar hemisphere. The clinical manifestations of cerebellar ataxia consist of irregularities in the rate, rhythm, amplitude, and force of voluntary movements.

A. Hypotonia. Cerebellar ataxia is commonly associated with hypotonia, which results in defective posture maintenance. Limbs are easily displaced by a relatively small force and, when shaken by the examiner, exhibit an increased range of excursion. The range of arm swing during walking may be similarly increased. Tendon reflexes take on a pendular quality, so that several oscillations of the limb may occur after the reflex is elicited, although neither the force nor the rate of the reflex is increased. When muscles are contracted against resistance that is then removed, the antagonist muscle fails to check the movement and compensatory muscular relaxation does not ensue promptly. This results in rebound movement of the limb.

B. Incoordination. In addition to hypotonia, cerebellar ataxia is associated with incoordination of voluntary movements. Simple movements are delayed in onset, and their rates of acceleration and deceleration are decreased. The rate, rhythm, amplitude, and force of movements fluctuate, producing a jerky appearance. Because these irregularities are most pronounced during initiation and termination of movement, their most obvious clinical manifestations include **terminal dysmetria,** or "overshoot," when the limb is directed at a target, and terminal **intention tremor** as the limb approaches the target. More complex movements tend to become decomposed into a succession of individual movements rather than a single smooth motor act (**asynergia**). Movements that involve rapid changes in direction or greater physiologic complexity, such as walking, are most severely affected.

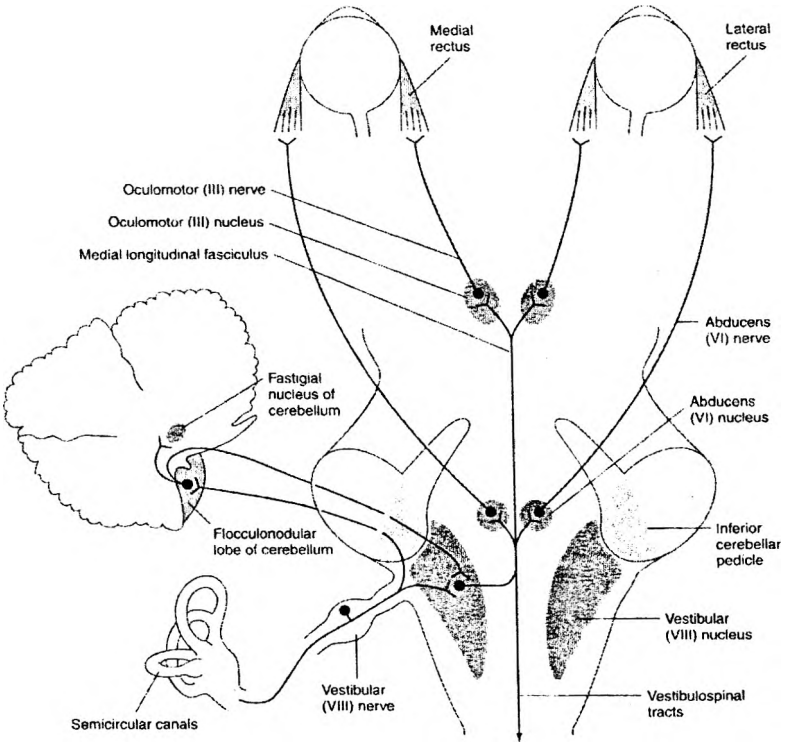


Fig. 3. Peripheral and central vestibular pathways. The vestibular nerve terminates in the vestibular nucleus of the brainstem and in midline cerebellar structures that also project to the vestibular nucleus. From here, bilateral pathways in the medial longitudinal fasciculus ascend to the abducens and oculomotor nuclei and descend to the spinal cord. (From R. Simon, M. Aminoff, D. Greenberg, 1999)

C. Associated Ocular Abnormalities. Because of the cerebellum's prominent role in the control of eye movements, ocular abnormalities are a frequent consequence of cerebellar disease. These include nystagmus and related ocular oscillations, gaze pareses, and defective saccadic and pursuit movements.

D. Anatomic Basis of Distribution of Clinical Signs. Various anatomic regions of the cerebellum are functionally distinct, corresponding to the somatotopic organization of their motor, sensory, visual, and auditory connections.

1. Midline lesions. The middle zone of the cerebellum – the vermis and flocculonodular lobe and their associated subcortical (fastigial) nuclei – is involved in the control of axial functions, including eye movements, head and trunk posture, stance, and gait. Midline cerebellar disease therefore results in a clinical syndrome characterized by nystagmus and other disorders of ocular motility, oscillation of the head and trunk (titubation), instability of stance, and gait ataxia. Selective involvement of the superior cerebellar vermis, as commonly occurs in alcoholic cerebellar degeneration, produces exclusively or primarily ataxia of gait, as would be predicted from the somatotopic map of the cerebellum.

2. Hemispheric lesions. The lateral zones of the cerebellum (cerebellar hemispheres) help to coordinate movements and maintain tone in the ipsilateral limbs. The hemispheres also have a role in regulating ipsilateral gaze. Disorders affecting one cerebellar hemisphere cause ipsilateral hemiataxia and hypotonia of the limbs as well as nystagmus and transient ipsilateral gaze paresis (an inability to look voluntarily toward the affected side). Cerebellar dysarthria may also occur with paramedian lesions in the left cerebellar hemisphere.

3. Diffuse lesions. Many cerebellar disorders – typically toxic, metabolic, and degenerative conditions – affect the cerebellum diffusely. The clinical picture in such states combines the features of midline and bilateral hemisphere disease.

Causes of cerebellar ataxia

Acute

Drug intoxications: ethanol, sedative-hypnotics, anticonvulsants, hallucinogens
Wernicke's encephalopathy
Vertebrobasilar ischemia or infarction
Cerebellar hemorrhage
Inflammatory disorders

Chronic

Multiple sclerosis
Alcoholic cerebellar degeneration
Phenytoin-induced cerebellar degeneration

Hypothyroidism
Paraneoplastic cerebellar degeneration
Hereditary spinocerebellar ataxias
Friedreich's ataxia
Ataxia-telangiectasia
Wilson's disease
Acquired hepatolenticular degeneration
Creutzfeldt-Jakob disease
Posterior fossa tumor
Posterior fossa malformations

Sensory Ataxia

Sensory ataxia results from disorders that affect the proprioceptive pathways in peripheral sensory nerves, sensory roots, posterior columns of the spinal cord, or medial lemnisci. Thalamic and parietal lobe lesions are rare causes of contralateral sensory hemiataxia. Sensations of joint position and movement (kinesthesis) originate in pacinian corpuscles and unencapsulated nerve endings in joint capsules, ligaments, muscle, and periosteum. Such sensations are transmitted via heavily myelinated A-fibers of primary afferent neurons, which enter the dorsal horn of the spinal cord and ascend uncrossed in the posterior columns. Proprioceptive information from the legs is conveyed in the medially located fasciculus gracilis, and that from the arms is conveyed in the more laterally situated fasciculus cuneatus. These tracts synapse on second-order sensory neurons in the nucleus gracilis and nucleus cuneatus in the lower medulla. The second-order neurons decussate as internal arcuate fibers and ascend in the contralateral medial lemniscus. They terminate in the ventral posterior nucleus of the thalamus, from which third-order sensory neurons project to the parietal cortex.

Numbness or tingling in the legs is common in patients with sensory ataxia. Clinical findings include defective joint position and vibration sense in the legs and sometimes the arms, unstable stance with Romberg's sign, and a gait of slapping or steppage quality. Because proprioceptive deficits may, to some extent, be compensated for by other sensory cues, patients with sensory ataxia may report that their balance is improved by watching their feet when they walk or by using a cane or the arm of a companion for support. They thus find that they are much more unsteady in the dark and may experience particular difficulty in descending stairs. Sensory ataxia from polyneuropathy or posterior column lesions typically affects the gait and legs in symmetric fashion; the arms are involved to a lesser extent or spared entirely. Vertigo, nystagmus, and dysarthria are characteristically absent.

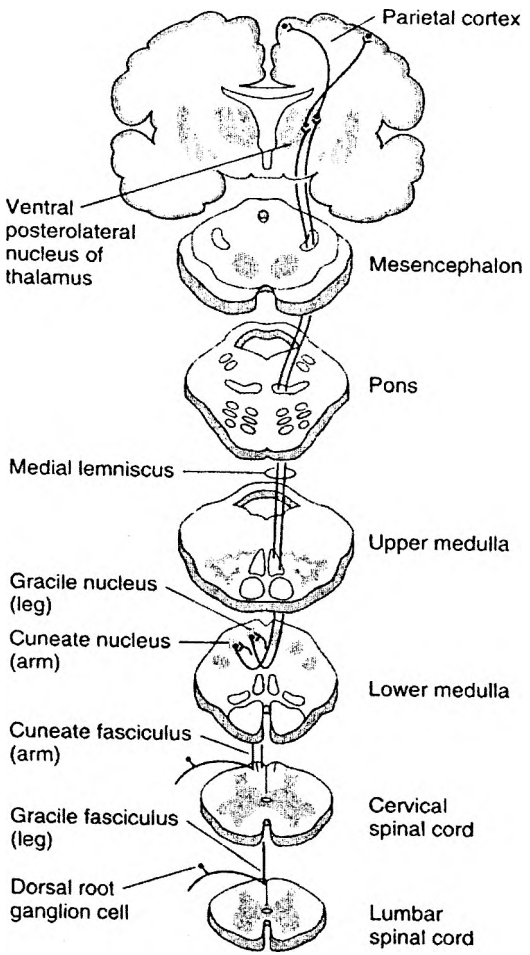


Fig. 4. Pathway mediating proprioceptive sensation. (From R. Simon, M. Aminoff, D. Greenberg, 1999)

Causes of sensory ataxia

Polyneuropathy'

Autosomal dominant sensory ataxic neuropathy
Cisplatin (cis-platinum)
Dejerine-Sottas disease
Diabetes
Diphtheria
Hypothyroidism
Immune-mediated neuropathies (GALOP syndrome, anti-MAG antibody syndrome, Miller Fisher syndrome, anti-GD1b antibody syndrome)
Isoniazid
Paraneoplastic sensory neuronopathy (anti-Hu antibodies)
Pyridoxine
Refsum's disease
Taxol

Myelopathy

Acute transverse myelitis
AIDS (vacuolar myelopathy)
Multiple sclerosis
Tumor or cord compression
Vascular malformations

Polyneuropathy or myelopathy

Friedreich's ataxia
Neurosyphilis (tabes dorsalis)
Nitrous oxide
Vitamin B_{12} deficiency
Vitamin E deficiency

Vestibular Ataxia

Ataxia associated with vertigo suggests a vestibular disorder, whereas numbness or tingling in the legs is common in patients with sensory ataxia. Vestibular ataxia can be produced by the same central and peripheral lesions that cause vertigo. Nystagmus is frequently present and is typically unilateral and most pronounced on gaze away from the side of vestibular involvement. Dysarthria does not occur. Vestibular ataxia is gravity-dependent: incoordination of limb movements cannot be demonstrated when the patient is examined lying down but becomes apparent when the patient attempts to stand or walk.

Stance & Gait

Observation of stance and gait is helpful in distinguishing between cerebellar, vestibular, and sensory ataxias. In any ataxic patient, the stance and gait are wide-based and unsteady, often associated with reeling or lurching movements.

A. Stance. The ataxic patient asked to stand with the feet together may show great reluctance or an inability to do so. With persistent urging, the patient may gradually move the feet closer together but will leave some space between them. Patients with sensory ataxia and some with vestibular ataxia are, nevertheless, ultimately able to stand with the feet together, compensating for the loss of one source of sensory input (proprioceptive or labyrinthine) with another (visual). This compensation is demonstrated when the patient closes the eyes, eliminating visual cues. With sensory or vestibular disorders, unsteadiness increases and may result in falling (Romberg's sign). With a vestibular lesion, the tendency is to fall toward the side of the lesion. Patients with cerebellar ataxia are unable to compensate for their deficit by using visual input and unstable on their feet whether the eyes are open or closed.

B. Gait.

1. The gait seen in cerebellar ataxia is wide based, often with a staggering quality that might suggest drunkenness. Oscillation of the head or trunk (titubation) may be present. If a unilateral cerebellar hemisphere lesion is responsible, there is a tendency to deviate toward the side of the lesion when the patient attempts to walk in a straight line or circle or marches in place with eyes closed. Tandem (heel-to-toe) gait, which requires walking with an exaggeratedly narrow base, is always impaired.

2. In sensory ataxia, the gait is also wide-based and tandem gait is poor. In addition, walking is typically characterized by lifting the feet high off the ground and slapping them down heavily (steppage gait) because of impaired proprioception. Stability may be dramatically improved by letting the patient use a cane or lightly rest a hand on the examiner's arm for support. If the patient is made to walk in the dark or with eyes closed, gait is much more impaired.

3. Gait ataxia may also be a manifestation of conversion disorder (conversion disorder with motor symptom or deficit) or malingering. Determining this can be particularly difficult, since isolated gait ataxia without ataxia of individual limbs can also be produced by diseases that affect the superior cerebellar vermis. The most helpful observation in identifying factitious gait ataxia is that such patients often exhibit wildly reeling or lurching movements from which they are able to recover without falling. In fact, recovery of balance from such awkward positions requires excellent equilibratory function.

Oculomotor (III), Trochlear (IV), Abducens (VI), & Acoustic (VIII) Nerves

Abnormalities of ocular and vestibular nerve function are typically present with vestibular disease and often present with lesions of the cerebellum.

A. Ocular Alignment. The eyes are examined in the primary position of gaze (looking directly forward) to detect mal alignment in the horizontal or vertical plane.

B. Nystagmus and Voluntary Eye Movements. The patient is asked to turn the eyes in each of the cardinal directions of gaze (left, up and left, down and left, right, up and right, down and right) to determine whether gaze paresis (impaired ability to move the two eyes coordinately in any of the cardinal directions of gaze) or gazeevoked nystagmus is present. Nystagmus – an abnormal involuntary oscillation of the eyes – is characterized in terms of the positions of gaze in which it occurs, its amplitude, and the direction of its fast phase. **Pendular nystagmus** has the same velocity in both directions of eye movement; **jerk nystagmus** is characterized by both fast (vestibular-induced) and slow (cortical) phases. The direction of jerk nystagmus is defined by the direction of the fast component. Fast voluntary eye movements (**saccades**) are elicited by having the patient rapidly shift gaze from one target to another placed in a different part of the visual field. Slow voluntary eye movements (pursuits) are assessed by having the patient track a slowly moving target such as the examiner's finger.

1. Peripheral vestibular disorders produce unidirectional horizontal jerk nystagmus that is maximal on gaze away from the involved side. Central vestibular disorders can cause unidirectional or bidirectional horizontal nystagmus, vertical nystagmus, or gaze paresis. Cerebellar lesions are associated with a wide range of ocular abnormalities, including gaze pareses, defective saccades or pursuits, nystagmus in any or all directions, and ocular dysmetria (overshoot of visual targets during saccadic eye movements).

2. Pendular nystagmus is usually the result of visual impairment that begins in infancy.

Motor System and Motor Co-ordination

Examination of motor function in the patient with a disorder of equilibrium should determine the pattern and severity of ataxia and disclose any associated pyramidal, extrapyramidal, or peripheral nerve involvement that might suggest a cause.

A. Ataxia and Disorders of Muscle Tone. Muscle tone is assessed as discussed in this chapter earlier. Truncal stability is assessed with the patient in the sitting position, and the limbs are examined individually.

1. Movement of the patient's arm is observed as his or her finger tracks back and forth between his or her own nose or chin and the examiner's finger. With mild cerebellar ataxia, an intention tremor characteristically appears near

the beginning and end of each such movement, and the patient may overshoot the target.

2. When the patient is asked to raise the arms rapidly to a given height – or when the arms, extended and outstretched in front of the patient, are displaced by a sudden force – there may be overshoot (rebound). Impaired ability to check the force of muscular contractions can also be demonstrated by having the patient forcefully flex the arm at the elbow against resistance-and then suddenly removing the resistance. If the limb is ataxic, continued contraction without resistance may cause the hand to strike the patient at the shoulder or in the face.

3. Ataxia of the legs is demonstrated by the supine patient's inability to run the heel of the foot smoothly up and down the opposite shin.

4. Ataxia of any limb is reflected by irregularity in the rate, rhythm, amplitude, and force of rapid successive tapping movements.

5. Hypotonia is characteristic of cerebellar disorders; with unilateral cerebellar hemispheric lesions, the ipsilateral limbs are hypotonic.

6. Extrapyramidal hypertonia (rigidity) occurs with cerebellar ataxia in Wilson's disease, acquired hepatocerebral degeneration, Creutzfeldt-Jakob disease, and certain types of olivopontocerebellar degeneration.

7. Ataxia with spasticity may be seen in multiple sclerosis, posterior fossa tumors or congenital anomalies, vertebrobasilar ischemia or infarction, olivopontocerebellar degeneration, Friedreich's and other hereditary ataxias, neurosyphilis, Creutzfeldt-Jakob disease, and vitamin B_{12} deficiency.

B. Weakness. The pattern of any weakness should be determined. Distal neuropathic weakness can be caused by disorders that produce sensory ataxia, such as polyneuropathies and Friedreich's ataxia. Paraparesis may be superimposed on ataxia in vitamin B_{12} deficiency, multiple sclerosis, foramen magnum lesions, or spinal cord tumors. Ataxic quadriparesis, hemiataxia with contralateral hemiparesis, or ataxic hemiparesis suggests a brainstem lesion.

C. Abnormal Involuntary Movements. Asterixis may occur in hepatic encephalopathy, acquired hepatocerebral degeneration, or other metabolic encephalopathies. Myoclonus occurs in the same conditions as asterixis and is a prominent manifestation of Creutzfeldt-Jakob disease. Chorea may be associated with cerebellar signs in Wilson's disease, acquired hepatocerebral degeneration, or ataxia-telangiectasia.

Sensory System

A. Joint Position Sense. In patients with sensory ataxia, joint position sense is always impaired in the legs and may be defective in the arms as well. Testing is accomplished by asking the patient to detect passive movement of the joints, beginning distally and moving proximally, to establish the upper level of deficit in each limb. Abnormalities of position sense can also be demonstrated by positioning one limb and having the patient, with eyes closed, place the opposite limb in the same position.

B. Vibratory Sense. Perception of vibratory sensation is frequently impaired in patients with sensory ataxia. The patient is asked to detect the vibration of a 128-Hz tuning fork placed over a bony prominence. Again, successively more proximal sites are tested to determine the upper level of the deficit in each limb or over the trunk. The patient's threshold for appreciating the vibration is compared with the examiner's own ability to detect it in the hand that holds the tuning fork.

Reflexes

Tendon reflexes are typically hypoactive, with a pendular quality, in cerebellar disorders; unilateral cerebellar lesions produce ipsilateral hyporeflexia. Hyporeflexia of the legs is a prominent manifestation of Friedreich's ataxia, tabes dorsalis, and polyneuropathies that cause sensory ataxia. Hyperactive reflexes and extensor plantar responses may accompany ataxia caused by multiple sclerosis, vitamin B_{12} deficiency, focal brainstem lesions, and certain olivopontocerebellar or spinocerebellar degenerations.

SENSORY SYSTEM AND SENSORY DISORDERS

An appreciation of the functional anatomy of the sensory components of the nervous system is essential for properly interpreting the history and clinical signs of patients with disorders of somatic sensation. As used here, the term includes sensations of touch or pressure, vibration, joint position, pain, temperature, and more complex functions that rely on these primary sensory modalities (eg, two-point discrimination, stereognosis, graphesthesia); it excludes special senses such as smell, vision, taste, and hearing.

FUNCTIONAL ANATOMY OF THE SENSORY PATHWAYS

The sensory pathway between the skin and deeper structures and the cerebral cortex involves three neurons, with two synapses occurring centrally. The cell body of the first sensory neuron of the spinal nerve is in the dorsal root ganglion. Each cell located there sends a peripheral process that terminates in a free nerve ending or encapsulated sensory receptor and a central process that enters the spinal cord. Sensory receptors are relatively specialized for particular sensations and, in addition to free nerve endings (pain), include Meissner's corpuscles, Merkel's corpuscles, and hair cells (touch); Krause's end-bulbs (cold); and Ruffini's corpuscles (heat). The location of the first central synapse depends upon the type of sensation but is either in the posterior gray column of the spinal cord or in the upward extension of this column in the lower brainstem.

The second synapse is located in the anterior part of the anterolateral nucleus of the thalamus, from which there is sensory radiation to the cerebral cortex. In the spinal cord, fibers mediating touch, pressure, and postural sensation ascend in the posterior white columns to the medulla, where they synapse in the gracile and cuneate nuclei. From these nuclei, fibers cross the midline and ascend in the medial lemniscus to the thalamus. Other fibers that mediate touch and those subserving pain and temperature appreciation synapse on neurons in the posterior horns of the spinal cord, particularly in the substantia gelatinosa. The fibers from these neurons then cross the midline and ascend in the anterolateral part of the cord; fibers mediating touch pass upward in the anterior spinothalamic tract, whereas pain and temperature fibers generally travel in the lateral spinothalamic tract. Fibers from this anterolateral system pass to the thalamic relay nuclei and to nonspecific thalamic projection nuclei and the mesencephalic reticular formation. Fibers from the lemniscal and anterolateral systems are joined in the brainstem by fibers subserving sensation from the head.

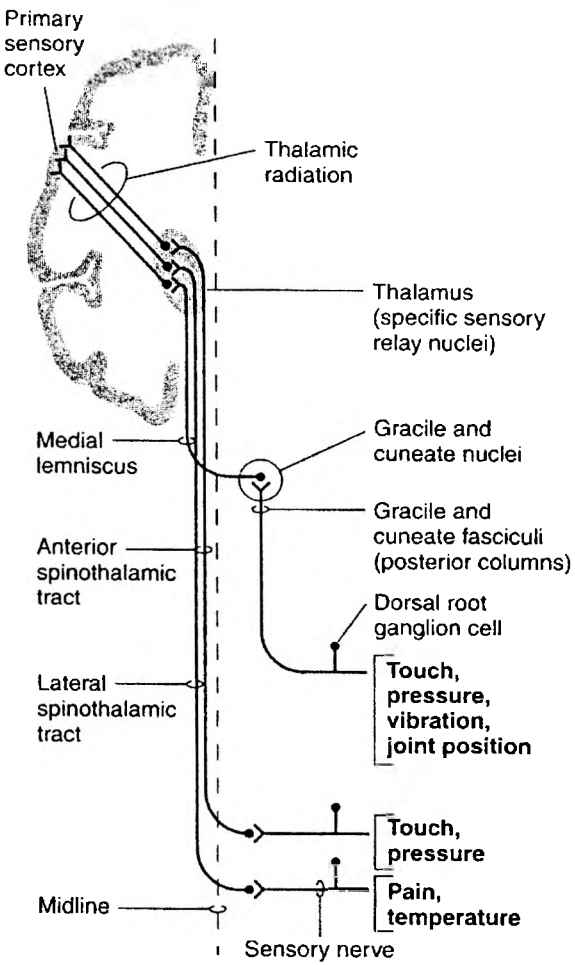


Fig. 5. Sensory pathways conveying touch, pressure, vibration, joint position, pain, and temperature sensation. (From R. Simon, M. Aminoff, D. Greenberg, 1999)

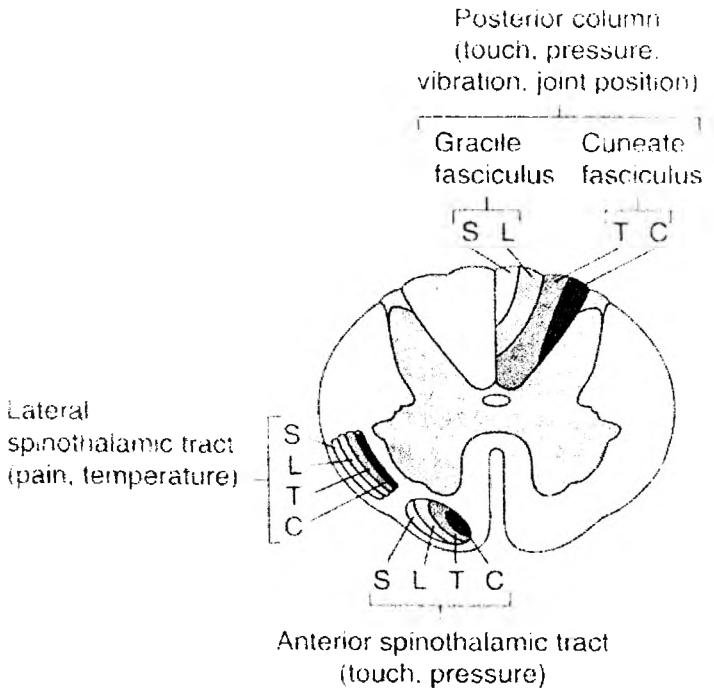


Fig. 6. Location and lamination of sensory pathways in the spinal cord. C (cervical), T (thoracic), L (lumbar), and S (sacral) indicate the level of origin of fibers within each tract. (From R. Simon, M. Aminoff, D. Greenberg, 1999)

Cephalic pain and temperature sensation are dependent upon the spinal nucleus of the trigeminal (V) nerve; touch, pressure, and postural sensation are conveyed mostly by the main sensory and mesencephalic nuclei of this nerve.

HISTORY

Sensory disturbances may consist of loss of sensation, the occurrence of abnormal sensations, or pain. The term paresthesia is used to denote abnormal spontaneous sensations, such as burning, tingling, or pins and needles. The term dysesthesia denotes any unpleasant sensation produced by a stimulus that is usually painless. The term numbness is often used by patients to describe a sense of heaviness, weakness, or deadness in the affected part of the body – and sometimes to signify any sensory impairment; its meaning must be clarified whenever the word is used.

In obtaining a history of sensory complaints, it is important to determine the location of the symptoms; the mode of onset and progression of the symptoms; whether the symptoms are constant or episodic in nature; whether any factors specifically produce, enhance, or relieve symptoms; and whether there are any accompanying symptoms.

The location of symptoms may provide a clue to their origin. For example, sensory disturbances involving all the limbs suggest peripheral neuropathy, a cervical cord or brainstem lesion, or a metabolic disturbance such as hyperventilation syndrome. Involvement of one entire limb – or of one side of the body – suggests a central (brain or spinal cord) lesion. A hemispheric or brainstem lesion may lead to lateralized sensory symptoms, but the face is also commonly affected. In addition, there may be other symptoms and signs, such as aphasia, apraxia, and visual field defects with hemispheric disease, or dysarthria, weakness, vertigo, diplopia, disequilibrium, and ataxia with brainstem disorders. Involvement of part of a limb or a discrete region of the trunk raises the possibility of a nerve or root lesion, depending upon the precise distribution. With a root lesion, symptoms may show some relationship to neck or back movements, and pain is often conspicuous.

The course of sensory complaints provides a guide to their cause. Intermittent or repetitive transient symptoms may represent sensory seizures, ischemic phenomena, or metabolic disturbances such as those accompanying hyperventilation. Intermittent localized symptoms that occur at a consistent time may suggest the diagnosis or an exogenous precipitating factor. For example, the pain and paresthesias of carpal tunnel syndrome (of median nerve compression) characteristically occur at night and awaken the patient from sleep.

EXAMINATION

In the investigation of sensory complaints, various modalities are tested in turn, and the distribution of any abnormality is plotted with particular reference to the normal root and peripheral nerve territories. Complete loss of touch appreciation is anesthesia, partial loss is hypesthesia, and increased sensitivity is hyperesthesia. The corresponding terms for pain appreciation are analgesia, hypalgesia, and hyperalgesia or hyperpathia; allodynia refers to the misperception of a trivial tactile sensation as pain.

1. PRIMARY SENSORY MODALITIES

Light Touch

The appreciation of light touch is evaluated with a wisp of cotton wool, which is brought down carefully on a small region of skin. The patient lies quietly, with the eyes closed, and makes a signal each time the stimulus is felt. The appreciation of light touch depends on fibers that traverse the posterior column of the spinal cord in the gracile (leg) and cuneate (arm) fasciculi ipsilaterally, passing to the medial lemniscus of the brainstem, and on fibers in the contralateral anterior spinothalamic tract.

Pinprick & Temperature

Pinprick appreciation is tested by asking the patient to indicate whether the point of a pin (not a hypodermic needle, which is likely to puncture the skin and draw blood) feels sharp or blunt. Appreciation of pressure or touch by the pinpoint must not be confused with the appreciation of sharpness. Temperature appreciation is evaluated by application to the skin of containers of hot or cold water. Pinprick and temperature appreciation depend upon the integrity of the lateral spinothalamic tracts. The afferent fibers cross in front of the central canal after ascending for two or three segments from their level of entry into the cord.

Deep Pressure

Deep pressure sensibility is evaluated by pressure on the tendons, such as the Achilles tendon at the ankle.

Vibration

Vibration appreciation is evaluated with a tuning fork (128 Hz) that is set in motion and then placed over a bony prominence; the patient is asked to indicate whether vibration, rather than simple pressure, is felt. Many elderly patients have impaired appreciation of vibration below the knees.

Joint Position

Joint position sense is tested by asking the patient to indicate the direction of small passive movements of the terminal interphalangeal joints of the fingers and toes. Patients with severe impairment of joint position sense may exhibit slow, continuous movement of the fingers (pseudoathetoid movement) when attempting to hold the hands outstretched with the eyes closed. For clinical purposes, both joint position sense and the ability to appreciate vibration are considered to depend on fibers carried in the posterior columns of the cord, although there is evidence that this is not true for vibration.

2. COMPLEX SENSORY FUNCTIONS

Romberg's Test

The patient is asked to assume a steady stance with feet together, arms outstretched, and eyes closed and is observed for any tendency to sway or fall. The test is positive (abnormal) if unsteadiness is markedly increased by eye closure-as occurs, for example, in tabes dorsalis. A positive test is indicative of grossly impaired joint position sense in the legs.

Two-Point Discrimination

The ability to distinguish simultaneous touch at two neighboring points depends upon the integrity of the central and peripheral nervous system, the degree of separation of the two points, and the part of the body that is stimulated. The patient is required to indicate whether he or she is touched by one or two compass points, while the distance between the points is varied in order to determine the shortest distance at which they are recognized as different points. The threshold for two-point discrimination approximates 4 mm at the fingertips and may be several centimeters on the back. When peripheral sensory function is intact, impaired two-point discrimination suggests a disorder affecting the sensory cortex.

Graphesthesia, Stereognosis, & Barognosis

Agraphesthesia, the inability to identify a number traced on the skin of the palm of the hand despite normal cutaneous sensation, implies a lesion involving the contralateral parietal lobe. The same is true of inability to distinguish between various shapes or textures by touch (astereognosis) or impaired ability to distinguish between different weights (abarognosis).

Bilateral Sensory Discrimination

In some patients with apparently normal sensation, simultaneous stimulation of the two sides of the body reveals an apparent neglect of (or inattention

to) sensation from one side, usually because of some underlying contralateral cerebral lesion.

SENSORY CHANGES, CLINICAL INTERPRETATION

It is important to determine the nature and distribution of any sensory change. Failure to find clinical evidence of sensory loss in patients with sensory symptoms must *never* be taken to imply that the symptoms have a psychogenic basis. Sensory symptoms often develop well before the onset of sensory signs.

Peripheral Nerve Lesions

A. Mononeuropathy. In patients with a lesion of a single peripheral nerve, sensory loss is usually less than would have been predicted on anatomic grounds because of overlap from adjacent nerves. Moreover, depending upon the type of lesion, the fibers in a sensory nerve may be affected differently. Compressive lesions, for example, tend to affect preferentially the large fibers that subserve touch.

B. Polyneuropathy. In patients with polyneuropathies, sensory loss is generally symmetric and is greater distally than proximally – as suggested by the term stocking-and-glove sensory loss. As a general rule the loss will have progressed almost to the knees before the hands are affected. Certain metabolic disorders (such as Tangier disease, a recessive trait characterized by the near absence of high-density lipoproteins) preferentially involve small nerve fibers that subserve pain and temperature appreciation. Sensory loss may be accompanied by a motor deficit and reflex changes.

Root Lesions

Nerve root involvement produces impairment of cutaneous sensation in a segmental pattern, but because of overlap there is generally no loss of sensation unless two or more adjacent roots are affected. Pain is often a conspicuous feature in patients with compressive root lesions. Depending on the level affected, there may be loss of tendon reflexes (C5-6, biceps and brachioradialis; C7-8, triceps; L3-4, knee; S1, ankle), and if the anterior roots are also involved, there may be weakness and muscle atrophy.

Spinal Cord Lesion

In patients with a spinal cord lesion, there may be a transverse sensory level. Physiologic areas of increased sensitivity do occur, however, at the costal margin, over the breasts, and in the groin, and these must not be taken as abnormal. Therefore, the level of a sensory deficit affecting the trunk is best determined by careful sensory testing over the back rather than the chest and abdomen.

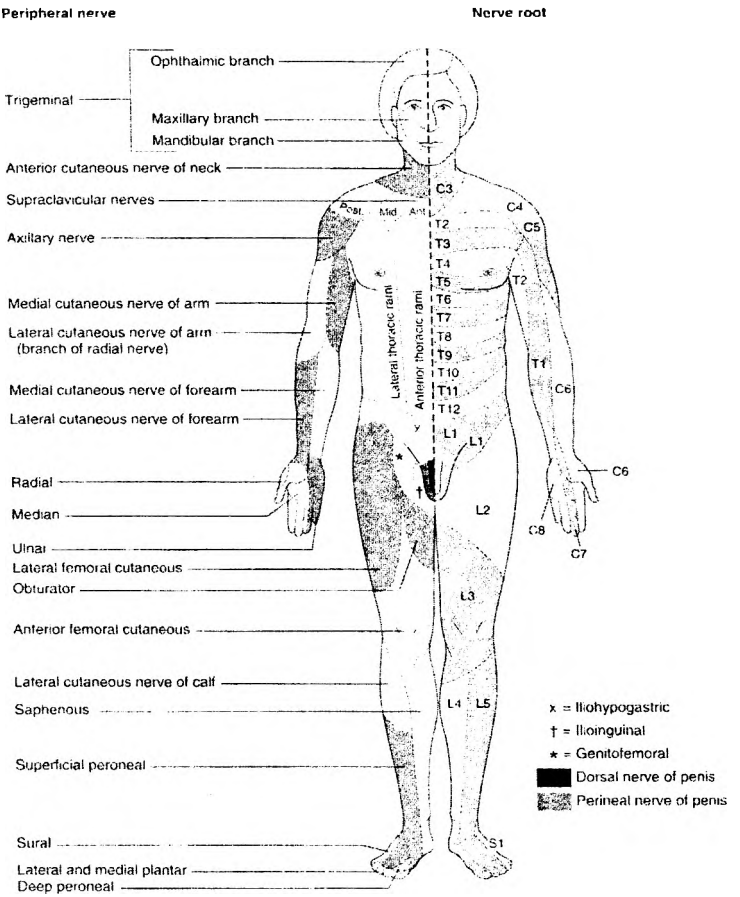


Fig. 7. Cutaneous innervation (anterior view). The segmental or radicular (nerve root) distribution is shown on the left side of the body, and the peripheral nerve distribution on the right side of the body. (From R. Simon, M. Aminoff, D. Greenberg, 1999)

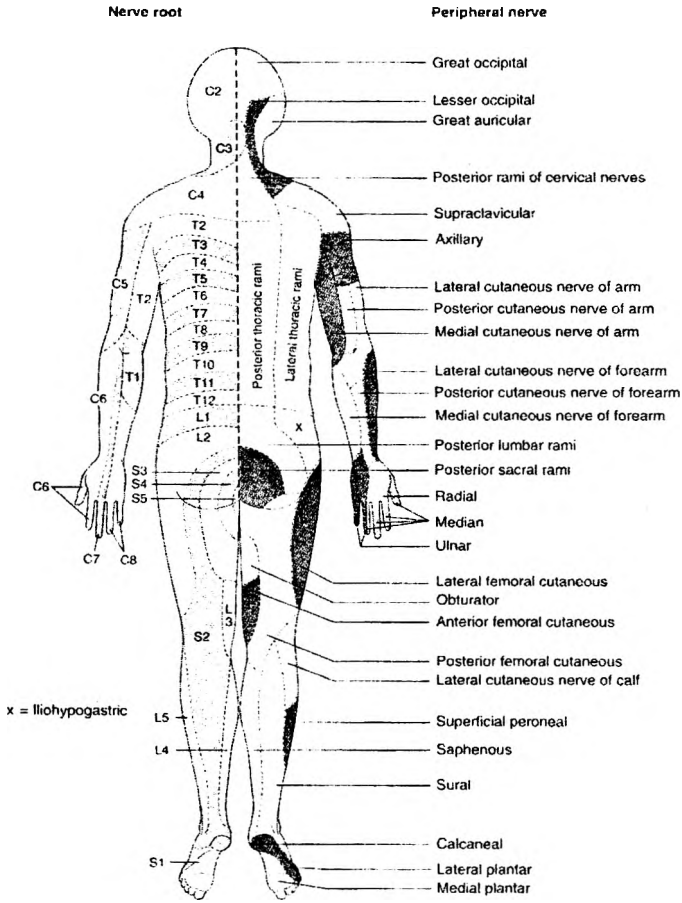


Fig. 8. Cutaneous innervation (posterior view). The segmental or radicular (nerve root) distribution is shown on the left side of the body, and the peripheral nerve distribution on the right side of the body. (From R. Simon, M. Aminoff, D. Greenberg, 1999)

A. Central Spinal Cord Lesion. With a central spinal cord lesion – such as occurs in syringomyelia, following trauma, and with certain cord tumors – there is characteristically a loss of pain and temperature appreciation with sparing of other modalities. This loss is due to the interruption of fibers conveying pain and temperature that cross from one side of the spinal cord to the spinothalamic tract on the other. Such a loss is usually bilateral, may be asymmetric, and involves only the fibers of the involved segments. It may be accompanied by lower motor neuron weakness in the muscles supplied by the affected segments and sometimes by a pyramidal and posterior column deficit below the lesion.

B. Anterolateral Spinal Cord Lesion. Lesions involving the anterolateral portion of the spinal cord (lateral spinothalamic tract) can cause contralateral impairment of pain and temperature appreciation in segments below the level of the lesion. The spinothalamic tract is laminated, with fibers from the sacral segments the outermost. Intrinsic spinal cord (intramedullary) lesions often spare the sacral fibers, while extramedullary lesions, which compress the spinal cord, tend to involve these fibers as well as those arising from more rostral levels.

C. Anterior Spinal Cord Lesion. With destructive lesions involving predominantly the anterior portion of the spinal cord, pain and temperature appreciation are impaired below the level of the lesion from lateral spinothalamic tract involvement. In addition, weakness or paralysis of muscles supplied by the involved segments of the spinal cord results from damage to motor neurons in the anterior horn. With more extensive disease, involvement of the corticospinal tracts in the lateral funiculi may cause a pyramidal deficit below the lesion. There is relative preservation of posterior column function. Ischemic myelopathies caused by occlusion of the anterior spinal artery take the form of anterior spinal cord lesions.

D. Posterior Spinal Column Lesion. A patient with a posterior column lesion may complain of a tight or bandlike sensation in the regions corresponding to the level of spinal involvement and sometimes also of paresthesias (like electric shocks) radiating down the extremities on neck flexion (Lhermitte's sign). There is loss of vibration and joint position sense below the level of the lesion, with preservation of other sensory modalities. The deficit may resemble that resulting from involvement of large fibers in the posterior roots.

E. Spinal Cord Hemisection. Lateral hemisection of the spinal cord leads to Brown-Sequard's syndrome. Below the lesion, there is an ipsilateral pyramidal deficit and disturbed appreciation of vibration and joint position sense, with contralateral loss of pain and temperature appreciation that begins two or three segments below the lesion.

Brainstem lesion

Sensory disturbances may be accompanied by a motor deficit, cerebellar signs, and cranial nerve palsies when the lesion is in the brainstem. In patients

with lesions involving the spinothalamic tract in the dorsolateral medulla and pons, pain and temperature appreciation are lost in the limbs and trunk on the opposite side of the body. When such a lesion is located in the medulla, it also typically involves the spinal trigeminal nucleus, impairing pain and temperature sensation on the same side of the face as the lesion. The result is a crossed sensory deficit that affects the ipsilateral face and contralateral limbs. In contrast, spinothalamic lesions above the spinal trigeminal nucleus affect the face, limbs, and trunk contralateral to the lesion. With lesions affecting the medial lemniscus, there is loss of touch and proprioception on the opposite side of the body. In the upper brainstem, the spinothalamic tract and medial lemniscus run together so that a single lesion may cause loss of all superficial and deep sensation over the contralateral side of the body.

Thalamic lesions

Thalamic lesions may lead to loss or impairment of all forms of sensation on the contralateral side of the body. Spontaneous pain, sometimes with a particularly unpleasant quality, may occur on the affected side. Patients may describe it as burning, tearing, knifelike, or stabbing, but often have difficulty characterizing it. Any form of cutaneous stimulation can lead to painful or unpleasant sensations. Such a thalamic syndrome (Dejerine-Roussy syndrome) can also occasionally result from lesions of the white matter of the parietal lobe or from cord lesions.

Sensory Cortex lesions

Disease limited to the sensory cortex impairs discriminative sensory function on the opposite side of the body. Thus, patients may be unable to localize stimuli on the affected side or to recognize the position of different parts of the body. They may not be able to recognize objects by touch or to estimate their size, weight, consistency, or texture. Cortical sensory disturbances are usually more conspicuous in the hands than in the trunk or proximal portions of the limbs.

PAIN SYNDROMES

Pain from infective, inflammatory, or neoplastic processes is a feature of many visceral diseases and may be a conspicuous component of certain neurologic or psychiatric diseases. It can also occur with no obvious cause.

In evaluating patients with pain, it is important to determine the level of the nervous system at which the pain arises and whether it has a primary neurologic basis. In taking the history, attention should be focused on the mode of onset, duration, nature, severity, and location of the pain; any associated symptoms; and factors that precipitate or relieve the pain.

Treatment depends on the underlying cause and clinical context of the pain and is discussed below. A brief comment is necessary, however, about stimulation-produced analgesia and, in particular, about spinal cord stimulation (previously known as dorsal column stimulation) and peripheral nerve stimulation. These approaches were based on principles encapsulated by the Gate Control theory, in which activation of large myelinated fibers was held to interrupt nociceptive transmission in the spinal cord, but their precise mechanism of action is uncertain. Spinal cord stimulation is known to affect certain neurotransmitter systems, particularly substance P and γ-aminobutyric acid (GABAergic) sytems.

Peripheral nerve pain

Pain arising from peripheral nerve lesions is usually localized to the region that is affected pathologically or confined to the territory of the affected nerve. It may have a burning quality, and when mixed (motor and sensory) nerves are involved, there may be an accompanying motor deficit. Painful peripheral neuropathies include those caused by diabetes, polyarteritis, alcoholic-nutritional deficiency states, and the various entrapment neuropathies. Treatment of pain associated with peripheral neuropathies is discussed in the section on diabetic neuropathy earlier.

The term causalgia correctly is used for the severe persistent pain, often burning in quality, that results from nerve trauma. Such pain often radiates to a more extensive territory than is supplied by the affected nerve and is associated with exquisite tenderness. Onset of pain may be at any time within the first 6 weeks or so after nerve injury. The cause is uncertain, but it has been attributed to ephaptic transmission between efferent sympathetic and afferent somatic fibers at the site of injury. Pain may be accompanied by increased sweating and vasoconstriction of the affected extremity, which is commonly kept covered up and still by the patient.

Reflex sympathetic dystrophy is a more general term that denotes sympathetically mediated pain syndromes precipitated by a wide variety of tissue injuries, including soft tissue trauma, bone fractures, and myocardial infarction.

Medical approaches to treatment include sympathetic blockade by injection of local anesthetics into the sympathetic chain or by regional infusion of reserpine or guanethidine. One such procedure may produce permanent cessation of pain-or repeated sympathetic blocks may be required. Surgical sympathectomy is beneficial in up to 75% of cases. Spinal cord stimulation has also been successful in some instances for the treatment of reflex sympathetic dystrophy or causalgia.

Radicular pain

Radicular pain is localized to the distribution of one or more nerve roots and is often exacerbated by coughing, sneezing, and other maneuvers that in-

crease intraspinal pressure. It is also exacerbated by maneuvers that stretch the affected roots. Passive straight leg raising leads to stretching of the sacral and lower lumbar roots, as does passive flexion of the neck. Spinal movements that narrow the intervertebral foramina can aggravate root pain. Extension and lateral flex ion of the head to the affected side may thus exacerbate cervical root symptoms. In addition to pain, root lesions can cause paresthesias and numbness in a dermatomal distribution; they can also cause segmental weakness and reflex changes, depending upon the level affected. Useful modes of treatment include immobilization, nonsteroidal anti-inflammatory drugs or other analgesics, and surgical decompression.

Thalamic pain

Depending upon their extent and precise location, thalamic lesions may lead to pain in all or part of the contralateral half of the body. The pain is of a burning nature with a particularly unpleasant quality that patients have difficulty describing. It is aggravated by emotional stress and tends to develop during partial recovery from a sensory deficit caused by the underlying thalamic lesion. Mild cutaneous stimulation may produce very unpleasant and painful sensations. This combination of sensory loss, spontaneous pain, and perverted cutaneous sensation has come to be called Dejerine-Roussy syndrome. Similar pain can be produced by a lesion that involves the parietal lobe or the sensory pathways at any point in the cord (posterior columns or spinothalamic tract) or in the brainstem. Treatment with analgesics, anticonvulsants (carbamazepine or phenytoin), or antidepressants and phenothiazines in combination is occasionally helpful.

Back and Neck pain

Spinal disease occurs most commonly in the neck or low back and can cause local or root pain or both. It can also lead to pain that is referred to other parts of the involved dermatomes. Pain from the lower lumbar spine, for example, is often referred to the buttocks. Conversely, pain may be referred to the back from the viscera, especially the pelvic organs. Local pain may lead to protective reflex muscle spasm, which in turn causes further pain and may result in abnormal posture, limitation of movement, and local spinal tenderness. The history may provide clues to the underlying cause, and physical examination will define any neurologic involvement.

DISTINCTION OF ORGANIC & PSYCHOGENIC SENSORY DISTURBANCES

Psychogenic disturbances of sensation may be associated with such psychiatric disturbances as conversion disorder. They may take any form but most

often are restricted to loss of cutaneous sensation. There may be several characteristic features.

Nonorganic sensory loss does not conform in its distribution to any specific neuroanatomic pattern. It may surround a bony landmark or involve an area defined by surface landmarks rather than innervation. Indeed, it is not uncommon for there to be an apparent loss of sensation in one or more extremities, with the margin occurring circumferentially in the axilla or groin; organic sensory loss with such a margin is unusual. Organic peripheral sensory loss over the trunk or face does not usually extend to the midline but stops 3-5 cm before it, because of overlap in the innervation on the two sides; with nonorganic disturbances, apparent sensory loss commonly stops precisely at the midline.

There is often a sudden transition between areas of nonorganic sensory loss and areas with normal sensation. By contrast, with organic disturbances, there is usually an area of altered sensation between insensitive areas and adjacent areas with normal sensibility.

In nonorganic disturbances, there may be a dissociated loss that is difficult to interpret on an anatomic basis. For example, there may be a total loss of pinprick appreciation but preserved temperature sensation. Moreover, despite the apparent loss of posterior column function, the patient may be able to walk normally or maintain the arms outstretched without difficulty or pseudo athetoid movements.

In nonorganic sensory disturbances, appreciation of vibration may be impaired on one side but not the other side of a bony midline structure, such as the skull or sternum. The vibrations are in fact conducted to both sides by the bone, so that even if there is a hemisensory disturbance, the vibrations are appreciated on either side in patients with organic sensory disorders.

Finally, it should be noted that sensory disturbances are often suggested to the patient by the examiner's own expectations. Such findings can be particularly misleading because they may be neuroanatomically correct. One helpful approach is to have the patient outline on the body the extent of any perceived sensory disturbance before formal sensory testing is undertaken.

DISORDERS OF CRANIAL NERVES FUNCTIONS

OLFACTORY NERVE (I) AND OLFACTION

Anatomy and physiology of olfaction

Odours, which must be volatile and soluble in water, are detected by specialized olfactory receptor cells in the olfactory epithelium, located in the mucous membrane of the upper and posterior parts of the nasal cavity (superior turbinates and nasal septum), and by the free nerve endings of the trigeminal nerve. The olfactory epithelium contains three cell types.

The olfactory receptor cell is a bipolar sensory neuron with a thin, single, dendritic knob which extends into the mucus layer of the nasal cavity. The mucus layer contains immunoglobulins A and M, lactoferrin, lysoenzyme, and odorant-binding proteins. These molecules are thought to prevent the passage of noxious pathogens into the intracranial cavity via the olfactory nerve. From the knob protrude 10-30 non-motile cilia which bear the specific membrane receptor proteins, and where signal transduction is initiated. When an odour binds to a receptor there is activation of a membrane-bound GTP-dependent adenylcyclase (G protein), which then activates a second messenger, leading to conformational changes in the transmembrane receptor and a series of intracellular events leading to the generation of axon potentials. Since the odour receptor cells respond to wide range of odorants, odour quality is presumably coded by some form of cross-fibre pattern. Very thin unmyelinated nerve axons leave the receptor cells and converge into small fascicles, enwrapped by Schwann cells, which pass through the cribriform plate of the ethmoid bone to the olfactory bulb. These axons collectively constitute the olfactory or first cranial nerve, and terminate within the olfactory glomeruli of the olfactory bulb. Here they form synaptic contacts with interneurons that have processes restricted to the bulb and with output neurons (mitral and internal tufted cells) that contribute axons to the lateral olfactory tract. From the olfactory tract axons project to terminate in primitive cortical areas, known as the primary olfactory cortex. In the human this probably includes small portions of the uncus, hippocampal gyrus, amygdaloid complex, and entorhinal cortex.

Olfactory disorders

Disturbances of olfaction can be grouped into four main subtypes:

1. Quantitative abnormalities: a total (general anosmia) or partial (partial anosmia) ability to detect olfactory sensations. There may also be a complete (general hyposmia) or incomplete (partial hyposmia) insensitivity to odorants, or heightened sensitivity (partial or total hyperosmia).

2. Qualitative abnormalities: distortions or illusions of smell (dysosmia or parosmia).

3. Olfactory delusions or hallucinations associated with disorders of the temporal lobe and psychiatric disease.

4. Olfactory agnosia in which there is an inability to recognize an odour sensation despite intact olfactory sensory processing, language, and general intellectual function.

Evaluation of olfactory function

In the clinical examination of olfactory function it is necessary to discriminate between deficits due to nasal obstruction, which prevent volatile substances from reaching the olfactory epithelium (transport olfactory loss), and neurogenic loss, which may be due to abnormalities of the receptors or their axons (sensory olfactory loss) or due to pathological processes affecting the central pathways. Transport olfactory loss can result from a variety of causes, including rhinitis, upper respiratory infection, polyps, sinusitis, and neoplasms. The symptoms of impaired olfactory detection, discrimination, or distortion of normal smells are no different to those accompanying sensory olfactory loss, which may be due to impaired receptor cell turnover resulting from radiation or chemotherapeutic drugs, or damage to the olfactory axons due to closed head injury, toxic substances, and viral infection.

It is therefore essential that, in addition to taking a full history and testing smell and taste, careful examination of the nose, mouth, and nasopharynx is undertaken. Examination of smell is usually carried out using a variety of familiar odiferous substances such as coffee, oil of peppermint, tobacco, oil of cloves, and vanilla. A bottle of each is held under one nostril with the other being occluded by a finger. The patient is asked whether or not he can detect an odour and, if so, whether or not he can identify it. If the odour can be detected even if it cannot be described, it may be assumed that the olfactory nerves are relatively intact. Malingering can be detected by using ammonia, which stimulates the trigeminal nerve. If the patient denies noticing the stimulus, the anosmia is likely to be bogus. A more refined assessment of olfaction can be performed using special standardized tests.

Disorders of olfaction and their interpretation

The most common causes of loss of smell are nasal and paranasal sinus disease, viral infection of the upper respiratory tract, and closed head injury.

Hypertrophy and hyperaemia of the nasal passages, from whatever cause, leads to hyposmia or anosmia, due to odours being unable to reach the olfactory epithelium. Chronic rhinitis and sinusitis of allergic, infective, or vasomotor origin are frequent causes. Nutritional and endocrinological disorders, such as thiamine deficiency, adrenal insufficiency, vitamin A deficiency, cirrhosis, renal failure, hypothyroidism, Cushing syndrome, may also have similar effects, due to sensorineural dysfunction. A frequent cause of hyposmia is heavy smoking. Infections due to influenza, herpes simplex, and hepatitis viruses can lead to hyposmia or anosmia due to destruction of the receptor cells, and recovery may not occur if the basal cells are also destroyed. There are several congenital diseases in which the receptor cells are absent or hypoplastic (Kallmann's syndrome, Turner's syndrome, and albinism).

Loss of smell in head trauma is usually due to the severing of the delicate axons of the receptor cells, as they pass through the cribriform plate, but may also occur due to damage of the olfactory bulb and possibly cerebral cortical injury. The incidence of smell dysfunction following head trauma is 5-10 per cent and is proportional to the severity of the injury. Anosmia or hyposmia may be unilateral or bilateral. Recovery of smell occurs in about a third of cases, but is unlikely to occur if the loss of smell has been present for more than 1 year after injury. The olfactory epithelium can be damaged by a variety of toxic agents, including organic solvents such as benzene, and drugs such as antimicrobial agents (ampicillin, griseofulvin, streptomycin, tetracyclines), anti-inflammatory agents (allopurinol, colchicine, gold, D-penicillamine, phenylbutazone), antiproliferative agents (methotrexate, vincristine, doxorubicin), and other drugs, including phenindione, amphetamines, cocaine, corticosteroids.

Impaired odour detection or discrimination has been described in Parkinson's disease and Alzheimer's disease. Alcoholics with Korsakoff's psychosis have a defect of odour discrimination, as have some patients with temporal lobe epilepsy. A similar deficit is found in patients in whom anterior temporal lobe or orbitofrontal cortical excision has been performed. Anosmia may be the first symptom of an olfactory groove meningioma, which may involve the olfactory bulb and tract, and extend posteriorly to involve the optic nerve, leading to atrophy (Foster Kennedy syndrome).

There is no specific treatment for patients with hyposmia or anosmia, unless there is a local, remediable cause. However, these patients are at potential risk from inhaling noxious fumes and failing to detect burning, so it is important to advise them of the necessary precautions. These should include the use of domestic smoke and gas detectors, and the provision of adequate ventilation in enclosed areas in which toxic solvents are being used.

The most common cause of parosmia, the distortion of normal smell, is a local nasopharyngeal condition such as sinusitis. Other causes include temporal lobe seizure, partial injuries of the olfactory bulb, and depression. The majority of patients have associated hyposmia or anosmia.

Olfactory hallucinations are always of central origin, and are most often due to temporal lobe seizures (uncinate seizures). Other causes include Alzheimer's disease, endogenous depression, schizophrenia, and alcohol withdrawal.

VISUAL & OCULAR MOTOR SYSTEMS (II, III, IV, VI)

Disorders that affect the ocular muscles, cranial nerves, or visual or ocular motor pathways in the brain produce a wide variety of neuro-ophthalmologic disturbances. Because the anatomic pathways of the visual and ocular motor systems traverse major portions of the brainstem and cerebral hemispheres, neuro-ophthalmologic signs are often of great value in the anatomic localization of neurologic disease, which in turn suggests possible etiologies. Symptoms most commonly involve vision (disorders of visual pathways) or eye movements (disorders of ocular motility) or both.

FUNCTIONAL ANATOMY OF THE VISUAL SYSTEM

Reception of Visual Information

Visual information enters the nervous system when light, refracted and focused by the lens, creates a visual image on the retina at the posterior pole of the eye. The action of the lens causes this image to be reversed in the horizontal and vertical planes. Thus, the superior portion of the visual image falls on the inferior retina and vice versa, and the temporal (lateral) and nasal (medial) fields are likewise reversed. The center of the visual field is focused at the fovea, where the retina's perceptual sensitivity is greatest. Within the retina, photoreceptor cells (rods and cones) transduce incident light into neuronal impulses, which are transmitted by retinal neurons to the optic (II) nerve. At this and all other levels of the visual system, the topographic relations of the visual field are preserved.

Peripheral Visual Pathways

Each optic nerve contains fibers from one eye, but the nasal (medial) fibers, conveying information from the temporal (lateral) visual fields, cross in the optic chiasm. As a result, each optic tract contains fibers not from one eye but from one half of the visual field. Because of this arrangement, prechiasmal lesions affect vision in the ipsilateral eye and retrochiasmal lesions produce defects in the contralateral half of the visual field of both eyes.

Central Visual Pathways

The optic tracts terminate in the lateral geniculate nuclei, where their neurons synapse on neurons that project through the optic radiations to the primary visual or calcarine cortex (area 17), located near the posterior poles of the occipital lobes, and visual association areas (areas 18 and 19). Here, too, the visual image is represented in such a way that its topographic organization is preserved. The central region of the visual field (macula) projects to the most poste-

rior portion of the visual cortex, while the inferior and superior parts of the field are represented above and below the calcarine fissure, respectively.

Vascular Supply

The vascular supply of the visual system is derived from the ophthalmic, middle cerebral, and posterior cerebral arteries; thus, ischemia or infarction in the territory of any of these vessels can produce visual field defects.

A. Retina. The retina is supplied by the central retinal artery, a branch of the ophthalmic artery that, in turn, branches from the internal carotid artery. Because the central retinal artery subsequently divides into superior and inferior retinal branches, vascular disease of the retina tends to produce altitudinal (ie, superior or inferior) visual field deficits.

B. Optic Nerve. The optic nerve receives arterial blood primarily from the ophthalmic artery and its branches.

C. Optic Radiations. As the optic radiations course backward toward the visual cortex, they are supplied by branches of the middle cerebral artery.

Ischemia or infarction in the distribution of the middle cerebral artery may thus cause loss of vision in the contralateral visual field.

D. Primary Visual Cortex. The principal source of arterial blood for the primary visual cortex is the posterior cerebral artery. Occlusion of one posterior cerebral artery produces blindness in the contralateral visual field, although the dual (middle and posterior cerebral) arterial supply to the macular region of the visual cortex may spare central (macular) vision. Because the posterior cerebral arteries arise together from the basilar artery, occlusion at the tip of the basilar artery can cause bilateral occipital infarction and complete cortical blindness-although, in some cases, macular vision is spared.

FUNCTIONAL ANATOMY OF THE OCULAR MOTOR SYSTEM

Extraocular Muscles

Movement of the eyes is accomplished by the action of six muscles attached to each globe. These muscles act to move the eye into each of six cardinal positions of gaze. Equal and opposed actions of these six muscles in the resting state place the eye in mid or primary position, ie, looking directly forward. When the function of one extraocular muscle is disrupted, the eye is unable to move in the direction of action of the affected muscle **(ophthalmoplegia)** and may deviate in the opposite direction because of the unopposed action of other extraocular muscles. When the eyes are thus misaligned, visual images of perceived objects fall on a different region of each retina, creating the illusion of double vision, or diplopia.

Cranial Nerves

The extraocular muscles are innervated by the oculomotor (III), trochlear (IV), and abducens (VI) nerves. Because of this differential innervation of the ocular muscles, the pattern of their involvement in pathologic conditions can help to distinguish a disorder of the ocular muscles per se from a disorder that is affecting a cranial nerve. Cranial nerves that control eye movement traverse long distances to pass from the brainstem to the eye; they are thereby rendered vulnerable to injury by a variety of pathologic processes.

A. Nerve III. The oculomotor nerve supplies the medial rectus, superior and inferior rectus, and inferior oblique muscles and carries fibers to the levator palpebrae (which raises the eyelid). It also supplies the parasympathetic fibers responsible for pupillary constriction. With a complete nerve III lesion, the eye is therefore partially abducted and there is an inability to adduct, elevate, and depress the eye; the eyelid droops (ptosis), and the pupil is nonreactive.

B. Nerve IV. The trochlear nerve innervates the superior oblique muscle. Lesions of this nerve result in defective depression of the adducted eye.

C. Nerve VI. Lesions of the abducens nerve cause lateral rectus palsy, with impaired abduction of the affected eye.

Cranial Nerve Nuclei

The nuclei of the oculomotor and trochlear nerves are located in the dorsal midbrain, ventral to the cerebral aqueduct (of Sylvius), while the abducens nerve nucleus occupies a similarly dorsal and periventricular position in the pons.

Lesions involving these nuclei give rise to clinical abnormalities similar to those produced by involvement of their respective cranial nerves; in some cases, nuclear and nerve lesions can be distinguished.

A. Nerve III Nucleus. Familiarity with the organization of the oculomotor nerve nucleus sometimes makes it possible to distinguish nuclear from nerve lesions. While each oculomotor nerve supplies muscles of the ipsilateral eye only, fibers to the superior rectus originate in the contralateral oculomotor nerve nucleus, and the levator palpebrae receives bilateral nuclear innervation. Thus, ophthalmoplegia affecting only one eye with ipsilateral ptosis or superior rectus palsy suggests oculomotor nerve disease, whereas ophthalmoplegia accompanied by bilateral ptosis or a contralateral superior rectus palsy is probably due to a nuclear lesion.

B. Nerve IV Nucleus. It is not possible to distinguish clinically between lesions of the trochlear nerve and those of its nucleus.

C. Nerve VI Nucleus. In disorders affecting the abducens nerve nucleus rather than the nerve itself, lateral rectus paresis is often associated with facial weakness, paresis of ipsilateral conjugate gaze, or a depressed level of consciousness. This is because of the proximity of the abducens nerve nucleus to the facial (VII) nerve fasciculus, pontine lateral gaze center, and ascending reticular activating system, respectively.

Supranuclear Control of Eye Movements

Supranuclear control of eye movements enables the two eyes to act in concert to produce version (conjugate gaze) or vergence (convergence and divergence) movements.

A. Brainstem Gaze Centers. Centers that control horizontal and vertical gaze are located in the pons and in the pretectal region of the midbrain, respectively, and receive descending inputs from the cerebral cortex that allow voluntary control of gaze. Each lateral gaze center, located in the paramedian pontine reticular formation (PPRF) adjacent to the abducens nerve nucleus, mediates ipsilateral conjugate horizontal gaze via its connections to the ipsilateral abducens and contralateral oculomotor nerve nucleus. A lesion in the pons affecting the PPRF therefore produces a gaze preference away from the side of the lesion-and toward the side of an associated hemiparesis, if present.

B. Cortical Input. The PPRF receives cortical input from the contralateral frontal lobe, which regulates rapid eye movements (saccades), and from the ipsilateral parieto-occipital lobe, which regulates slow eye movements (pursuits). Therefore, a destructive lesion affecting the frontal cortex interferes with the mechanism for contralateral horizontal gaze and may result in a gaze preference toward the side of the lesion (and away from the side of associated hemiparesis). By contrast, an irritative (seizure) focus in the frontal lobe may cause gaze away from the side of the focus.

NEURO-OPHTHALMOLOGIC EXAMINATION

Visual Acuity

A. Assessment. To assess visual acuity from a neurologic standpoint, vision is tested under conditions that eliminate refractive errors. Therefore, patients who wear glasses should be examined while wearing them (a pinhole can be substituted if the corrective lenses usually worn are not available at the time of testing). Visual acuity must be assessed for each eye separately. Distant vision is tested using a Snellen eye chart, with the patient 6 m (20 ft) away. Near vision is tested with the Rosenbaum pocket eye chart held about 36 cm (14 in) from the patient. In each case, the smallest line of print that can be read is noted.

B. Recording. Visual acuity is expressed as a fraction (eg, 20/20, 20/40, 20/200). The numerator is the distance (in feet) from the test figures at which the examination is performed, and the denominator is the distance (in feet) at which figures of a given size can be correctly identified by persons with normal vision. For example, if a patient standing 20 ft away from the eye chart is unable to identify figures that can normally be seen from that distance but can identify the larger figures that would be visible 40 ft away with normal acuity, the visual acuity is recorded as 20/40. If the patient can read most of a given line but

makes some errors, acuity may be recorded as 20/40-1, for example, indicating that all but one letter on the 20/40 line were correctly identified. When visual acuity is markedly reduced, it can still be quantified, though less precisely, in terms of the distance at which the patient can count fingers (CF), discern hand movement (HM), or perceive light. If an eye is totally blind, the examination will reveal no light perception (NLP).

C. Red-Green Color Vision. Red-green color vision is often disproportionately impaired in optic nerve lesions and can be tested with colored objects such as pens or hatpins or with color vision plates.

Visual Fields

Evaluating the visual fields can be a lengthy and tedious procedure if conducted in an undirected fashion. Familiarity with the common types of visual field defects is important if testing is to be reasonably rapid and yield useful information. The most common visual field abnormalities are illustrated in Figure.

A. Extent of Visual Fields. The normal monocular visual field subtends an angle of about 160 degrees in the horizontal plane and about 135 degrees in the vertical plane. With binocular vision, the horizontal range of vision exceeds 180 degrees.

B. Physiologic Blind Spot. Within the normal field of each eye is a 5-degree blind spot, corresponding to the optic disk, which lacks receptor cells.

C. Measurement Techniques. Numerous techniques exist for measuring the visual field – which, like visual acuity, must be examined separately for each eye.

1. The simplest method for visual field testing is the confrontation technique. The examiner stands at about arm's length from the patient, with the eyes of both patient and examiner aligned in the horizontal plane. The eye not being tested is covered by the patient's hand or an eye patch. The examiner closes the eye opposite the patient's covered eye, and the patient is instructed to fix on the examiner's open eye. Now the monocular fields of patient and examiner are superimposed, which allows comparison of the patient's field with the examiner's presumably normal field. The examiner uses the index fingers of both hands to locate the boundaries of the patient's field, moving them slowly inward from the periphery in all directions until the patient detects them. The boundaries are then defined more carefully by determining the farthest peripheral sites at which the patient can detect slight movements of the fingertips or the white head of a pin. The patient's blind spot can be located in the region of the examiner's own blind spot, and the sizes of these spots can be compared using a pin with a white head as the target. The procedure is then repeated for the other eye.

2. Subtle field defects may be detected by asking the patient to compare the brightness of colored objects presented at different sites in the field or by measuring the fields using a pin with a red head as the target.

3. In young children, the fields may be assessed by standing behind the child and bringing an attention-getting object, such as a toy, forward around the child's head in various directions until it is first noticed.

4. A gross indication of visual field abnormalities may be obtained in obtunded patients by determining whether they blink in response to a visual threat – typically the examiner's finger – brought toward the patient's eye in various regions of the field.

5. While many visual field deficits are detectable by these screening procedures, more precise mapping of the fields requires the use of one of many perimetry techniques. In tangent screen testing, the patient typically sits I m from the screen with one eye covered, and the examiner places pins of various sizes and colors on the surface of the screen. The field is plotted for each eye, indicating the sizes of the test objects and the distance of the patient from the screen.

Ophthalmoscopy

A. Preparation of the Patient. Ophthalmoscopic examination of the optic fundus is particularly important in evaluating neuro-ophthalmologic disorders that affect the retina or optic disk and in the evaluation of patients with a suspected increase in intracranial pressure. The examination should be conducted in a dark room so that the pupils are dilated; in some patients, the use of mydriatic (sympathomimetic or anticholinergic) eye drops is necessary. In the latter case, visual acuity and pupillary reflexes should always be assessed before instilling the drops. Mydriatic agents should be avoided in patients with glaucoma and in situations-such as impending or ongoing transtentorial herniation-in which the state of pupillary reactivity is an important guide to management.

B. Examination of the Fundus. Familiarity with the normal appearance of the optic fundus is necessary if abnormalities are to be appreciated.

1. Optic disk

a. Normal appearance. The optic disk is usually easily recognizable as a yellowish, slightly oval structure situated nasally at the posterior pole of the eye. The temporal side of the disk is often paler than the nasal side. The disk margins should be sharply demarcated, though the nasal edge is commonly somewhat less distinct than the temporal edge. The disk is normally in the same plane as the surrounding retina.

b. Optic disk swelling. Among the many ophthalmoscopic findings that provide useful diagnostic information, the abnormality that most often requires prompt interpretation and attention is optic nerve swelling (papilledema). While this condition implies increased intracranial pressure, it must be differentiated from swelling that is due to other causes, such as local inflammation (papillitis) and ischemic optic neuropathy. In making this distinction, it is most helpful to bear in mind that papilledema is almost always bilateral; it does not typically impair vision, except for enlargement of the blind spot; and it is not associated

with eye pain. Papilledema can also be simulated by disk abnormalities such as drusen (colloid or hyaline bodies).

Increased intracranial pressure is thought to cause papilledema by transmitting the increased pressure through the intravaginal space surrounding the optic nerve. Because this compartment communicates with the subarachnoid space, disorders associated with increased intracranial pressure that also obstruct the subarachnoid space, such as meningitis, are less likely to cause papilledema. The ophthalmoscopic changes in papilledema typically develop over days or weeks but may become apparent within hours following a sudden increase in intracranial pressure-as, for example, following intracranial hemorrhage. In early papilledema, the retinal veins appear engorged and spontaneous venous pulsations are absent. The disk may be hyperemic, and linear hemorrhages may be seen at its borders. The disk margins become blurred, with the temporal edge last to be affected. In fully developed papilledema, the optic disk is elevated above the plane of the retina.

c. Optic disk pallor. Optic disk pallor with impaired visual acuity, visual fields, or pupillary reactivity is associated with a wide variety of disorders that affect the optic nerve, including inflammatory conditions, nutritional deficiencies, and heredodegenerative diseases. Note that a pale optic disk with normal visual function can occur as a congenital variant.

2. Arteries and veins. To determine the caliber of the retinal arteries and veins, they are observed at the point where they arise from the disk and pass over its edges onto the retina. Observations include whether they are easily visible throughout their course, whether they appear engorged, and whether spontaneous venous pulsations are present. The remainder of the visible retina is inspected, noting the presence of hemorrhages, exudates, or other abnormalities.

3. Macula. The macula, a somewhat paler area than the rest of the retina, is located about two disk diameters temporal to the temporal margin of the optic disk. It can be visualized quickly by having the patient look at the light from the ophthalmoscope. Ophthalmoscopic examination of the macula can reveal abnormalities related to visual loss from age-related macular degeneration, from macular holes, or from hereditary cerebromacular degenerations.

Pupils

A. Size. Assessing the size and reactivity of the pupils provides an evaluation of nervous system pathways from the optic nerve to the midbrain. The normal pupil is round, regular, and centered within the iris; its size varies with age and with the intensity of ambient light. In a brightly illuminated examining room, normal pupils are about 3 mm in diameter in adults. They are often smaller in the elderly and commonly 5 mm or more in diameter in children. Pupillary size may be asymmetric in as much as 20% of the population (physiologic anisocoria), but the difference in size is not more than I mm. Symmetrically

rapid constriction in response to a bright light indicates that the size difference is not due to oculomotor nerve compression.

B. Reaction to Light. Direct (ipsilateral) and consensual (contralateral) pupillary constriction in response to a bright light shined in one eye demonstrates the integrity of the pathways. Normally, the direct response to light is slightly brisker and more pronounced than the consensual response.

C. Reaction to Accommodation. When the eyes converge to focus on a nearer object, the pupils normally constrict. The reaction to accommodation is tested by having the patient focus alternately on a distant object and a finger held just in front of his or her nose.

D. Pupillary Abnormalities:

1. Nonreactive pupils. Unilateral disorders of pupillary constriction are seen with local disease of the iris (trauma, iritis, glaucoma), oculomotor nerve compression (tumor, aneurysm), and optic nerve disorders (optic neuritis, multiple sclerosis).

2. Light-near dissociation. Impaired pupillary reactivity to light with preserved constriction during accommodation (light-near dissociation) is usually bilateral and may result from neurosyphilis, diabetes, optic nerve disorders, and tumors compressing the midbrain tectum.

3. Argyll Robertson pupils. These pupils are small, poorly reactive to light, often irregular in shape, and frequently unequal in size; they show light-near dissociation. Neurosyphilis is the usual cause.

4. Tonic pupil. The tonic (Adie's) pupil is larger than the contralateral unaffected pupil and reacts sluggishly to changes in illumination or accommodation. Since the tonic pupil does eventually react, anisocoria becomes less marked during the time of the examination. This abnormality is most commonly a manifestation of a benign, often familial disorder that frequently affects young women (Holmes-Adie syndrome) and may be associated with depressed deep tendon reflexes (especially in the legs), segmental anhidrosis (localized lack of sweating), orthostatic hypotension, or cardiovascular autonomic instability. The condition may be bilateral. The pupillary abnormality may be caused by degeneration of the ciliary ganglion, followed by aberrant reinnervation of the pupilloconstrictor muscles.

5. Horner's syndrome. Horner's syndrome results from a lesion of the central or peripheral sympathetic nervous system and consists of a small (miotic) pupil associated with mild ptosis and sometimes loss of sweating (anhidrosis).

a. Oculosympathetic pathways. The sympathetic pathway controlling pupillary dilation consists of an uncrossed three-neuron arc: hypothalamic neurons, the axons of which descend through the brainstem to the intermediolateral column of the spinal cord at the Tllevel; preganglionic sympathetic neurons projecting from the spinal cord to the superior cervical ganglion; and postganglionic sympathetic neurons that originate in the superior cervical ganglion, ascend in

the neck along the internal carotid artery, and enter the orbit with the first (ophthalmic) division of the trigeminal (V) nerve. Homer's syndrome is caused by interruption of these pathways at any site.

b. Clinical features. The lesions-and the pupillary abnormality produced-are usually unilateral. The pupillary diameter on the involved side is typically reduced by 0.5-1 mm compared with the normal side. This inequality is most marked in dim illumination and in other situations in which the pupils are normally dilated, such as during a painful stimulus or startle. The pupillary abnormality is accompanied by mild to moderate ptosis (see below) of the upper lid (as opposed to the pronounced ptosis with oculomotor nerve lesions), often associated with elevation of the lower lid. When Homer's syndrome has been present since infancy, the ipsilateral iris is lighter and blue (heterochromia iridis).

Deficits in the pattern of sweating, which are most prominent in acute-onset Homer's syndrome, can help localize the lesion. If sweating is decreased on an entire half of the body and face, the lesion is in the central nervous system. Cervical lesions produce anhidrosis of the face, neck, and arm only. Sweating is unimpaired if the lesion is above the bifurcation of the carotid artery.

6. Relative afferent pupillary defect (Marcus Gunn pupil). In this condition, one pupil constricts less markedly in response to direct illumination than to illumination of the contralateral pupil, whereas normally the direct response is greater than the consensual response. The abnormality is detected by rapidly moving a bright flashlight back and forth between the eyes while continuously observing the suspect pupil (Gunn's pupillary test). Relative afferent pupillary defect is commonly associated with disorders of the ipsilateral optic nerve, which interrupt the afferent limb and affect the pupillary light reflex. Such disorders also commonly impair vision (especially color vision) in the involved eye.

Optokinetic Response

Optokinetic nystagmus consists of eye movements elicited by sequential fixation on a series of targets passing in front of a patient's eyes, such as telephone poles seen from a moving train. For clinical testing, a revolving drum with vertical stripes or a vertically striped strip of cloth moved across the visual field is used to generate these movements. Testing produces a slow following phase in the direction of the target's movement, followed by a rapid return jerk in the opposite direction. The slow (pursuit) phase tests ipsilateral parieto-occipital pathways; the rapid (saccadic) movement tests pathways originating in the contralateral frontal lobe. The presence of an optokinetic response reflects the ability to perceive movement or contour and is sometimes useful for documenting visual perception in newborns or in psychogenic blindness. Visual acuity required to produce the optokinetic response is minimal, however (20/400, or finger counting at 3-5 ft). Unilateral impairment of the optokinetic response may be found when targets are moved toward the side of a parietal lobe lesion.

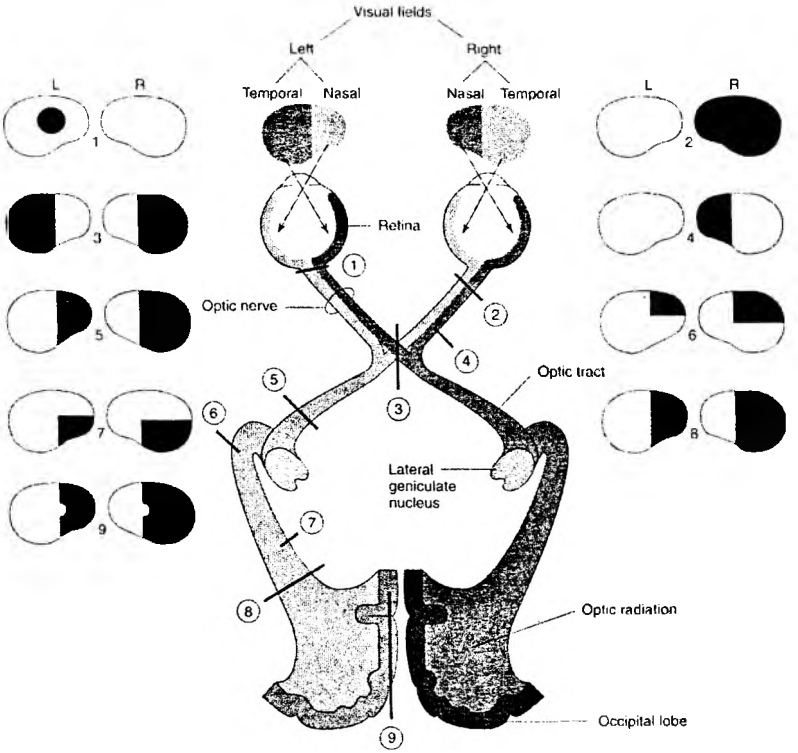


Fig. 9. Common visual field defects and their anatomical bases. 1. **Central scotoma** caused by inflammation of the optic disk (optic neuritis) or optic nerve (retrobulbar neuritis). 2. **Total blindness of the right** eye from a complete lesion of the right optic nerve. 3. **Bitemporal hemianopia** caused by pressure exerted on the optic chiasm by a pituitary tumor. 4. **Right nasal hemianopia** caused by a perichiasmal lesion (eg, calcified internal carotid artery). 5. **Right homonymous hemianopia** from a lesion of the left optic tract. 6. **Right homonymous superior quadrantanopia** caused by partial involvement of the optic radiation by a lesion in the left temporal lobe (Meyer's loop). 7. **Right homonymous inferior quadrantanopia** caused by partial involvement of the optic radiation by a lesion in the left parietal lobe. 8. **Right homonymous hemianopia** from a complete lesion of the left optic radiation. (A similar defect may also result from lesion 9.) 9. **Right homonymous hemianopia (with macular sparing)** resulting from posterior cerebral artery occlusion. (From R. Simon, M. Aminoff, D. Greenberg, 1999)

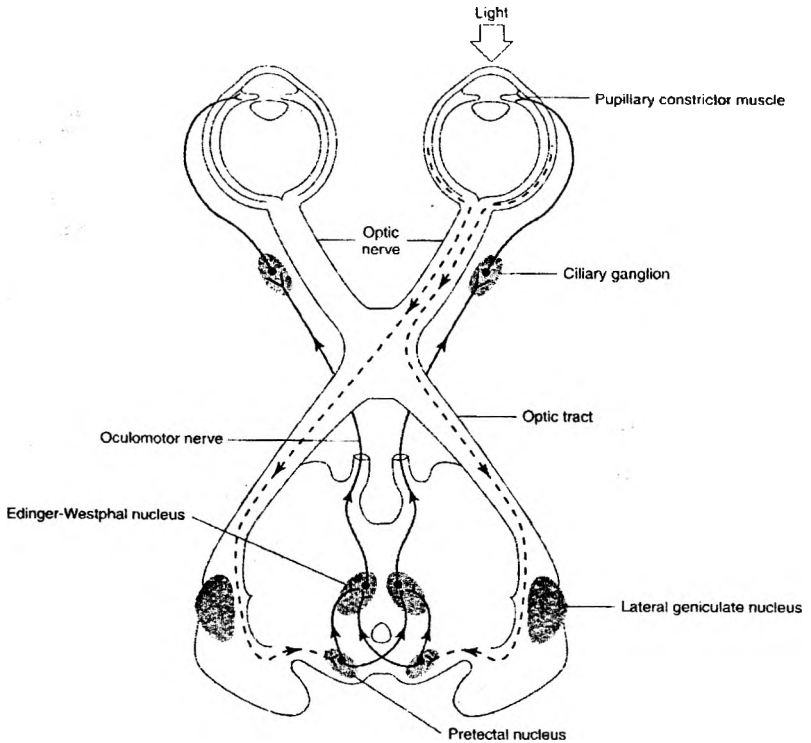


Fig. 10. Anatomic basis of the pupillary light reflex. The afferent visual pathways from the retina to the pretectal nuclei of the midbrain are represented by dashed lines and the efferent pupilloconstrictor pathways from the midbrain to the retinas by solid lines. Note that illumination of one eye results in bilateral pupillary constriction. (From R. Simon, M. Aminoff, D. Greenberg, 1999)

Eyelids

The eyelids (palpebrae) should be examined with the patient's eyes open. The distance between the upper and lower lids (interpalpebral fissure) is usually about 10 mm and equal in both eyes, though physiological asymmetries do occur. The position of the inferior margin of the upper lid relative to the superior border of the iris should be noted in order to detect drooping (ptosis) or abnormal elevation of the eyelid (lid retraction). The upper lid normally covers 1-2 mm of the iris.

Unilateral ptosis is seen with paralysis of the levator palpebrae muscle itself, lesions of the oculomotor nerve or its superior branch, and Homer's syndrome. In the last condition, ptosis is customarily associated with miosis and may be momentarily overcome by effortful eye opening.

Bilateral ptosis suggests disease affecting the oculomotor nerve nucleus; a disorder of the neuromuscular junction, such as myasthenia gravis; or a disorder of muscle, such as myotonic, ocular, or oculopharyngeal dystrophy.

Lid retraction (abnormal elevation of the upper lid) is seen in hyperthyroidism; in Parinaud's syndrome, it is caused by tumors in the pineal region.

Exophthalmos

Abnormal protrusion of the eye from the orbit (exophthalmos or proptosis) is best detected by standing behind the seated patient and looking down at his or her eyes. The causes include hyperthyroidism, orbital tumor or pseudotumor, and carotid artery-cavernous sinus fistula. A bruit may be audible on auscultation over the proptotic eye in patients with carotid artery-cavernous sinus fistula or other vascular anomalies.

Eye Movements

A. Ocular Excursion and Gaze. Ocular palsies and gaze palsies are detected by having the patient gaze in each of the six cardinal positions. If voluntary eye movement is impaired or the patient is unable to cooperate with the examination (eg, is comatose), reflex eye movements can be induced by one of two maneuvers. The doll's head (oculocephalic) maneuver is performed by rotating the head horizontally, to elicit horizontal eye movements, and vertically, to elicit vertical movements. The eyes should move in the direction opposite to that of head rotation. This may be an inadequate stimulus for inducing eye movements, however, and the reflex may be overridden in conscious patients. Caloric (oculovestibular) stimulation is a more potent stimulus and is performed by irrigating the tympanic membrane with cold (30°C) or warm (44°C) water. Otoscopic examination should always be undertaken before this maneuver is attempted: it is contraindicated if the tympanic membrane is perforated. In conscious patients, unilateral cold water irrigation produces nystagmus with the fast phase directed away from the irrigated side. Because this procedure may pro-

duce discomfort and nausea or vomiting, only small volumes (eg, 1 mL) of water should be used in conscious patients. In comatose patients with intact brainstem function, unilateral cold water irrigation results in tonic deviation of the eyes toward the irrigated side. Bilateral irrigation with cold water causes tonic downward deviation, whereas bilateral stimulation with warm water induces tonic upward deviation. An absent or impaired response to caloric stimulation with large volumes (eg, 50 mL) of cold water is indicative of peripheral vestibular disease, a structural lesion in the posterior fossa (cerebellum or brainstem), or intoxication with sedative drugs. If limitations in movement are observed, the muscles involved are noted and the nature of the abnormality is determined according to the following scheme.

1. Ocular palsy. This weakness of one or more eye muscles results from nuclear or infranuclear (nerve, neuromuscular junction, or muscle) lesions. An ocular palsy cannot be overcome by caloric stimulation of reflex eye movement. Nerve lesions produce distinctive patterns of ocular muscle involvement.

a. Oculomotor (III) nerve palsy. A complete lesion of the oculomotor nerve produces closure of the affected eye because of impaired levator function. Passively elevating the paralyzed lid shows the involved eye to be laterally deviated because of the unopposed action of the lateral rectus muscle, which is not innervated by the oculomotor nerve. Diplopia is present in all directions of gaze except for lateral gaze toward the side of involvement. The pupil's function may be normal (pupillary sparing) or impaired.

b. Trochlear (IV) nerve palsy. With trochlear nerve lesions, which paralyze the superior oblique muscle, the involved eye is elevated during primary (forward) gaze; the extent of elevation increases during adduction and decreases during abduction. Elevation is greatest when the head is tilted toward the side of the involved eye and abolished by tilt in the opposite direction (Bielschowsky's head-tilt test). Diplopia is most pronounced when the patient looks downward with the affected eye adducted (as in looking at the end of one's nose). Spontaneous head tilting, intended to decrease or correct the diplopia, is present in about half the patients with unilateral palsies and in an even greater number with bilateral palsies.

c. Abducens (VI) nerve palsy. An abducens nerve lesion causes paralysis of the lateral rectus muscle, resulting in adduction of the involved eye at rest and failure of attempted abduction. Diplopia occurs on lateral gaze to the side of the affected eye.

2. Gaze palsy. Gaze palsy is the diminished ability of a pair of yoked muscles (muscles that operate in concert to move the two eyes in a given direction) to move the eyes in voluntary gaze; it is caused by supranuclear lesions in the brainstem or cerebral hemisphere. Gaze palsy, unlike ocular palsies, affects both eyes and can usually be overcome by caloric stimulation. Its pathophysiology and causes are discussed more fully in the section on gaze palsy. Mild impairment of upgaze is not uncommon in asymptomatic elderly subjects.

3. Internuclear ophthalmoplegia. This disorder results from a lesion of the medial longitudinal fasciculus, an ascending pathway in the brainstem that projects from the abducens to the contralateral oculomotor nerve nucleus. As a consequence, the actions of the abducens and oculomotor nerves during voluntary gaze or caloric-induced movement are uncoupled. Excursion of the abducting eye is full, but adduction of the contralateral eye is impaired. Internuclear ophthalmoplegia cannot be overcome by caloric stimulation; it can be distinguished from oculomotor nerve palsy by noting preservation of adduction with convergence.

4. One-and-a-half syndrome. A pontine lesion affecting both the medial longitudinal fasciculus and the ipsilateral paramedian pontine reticular formation (lateral gaze center) produces a syndrome that combines internuclear ophthalmoplegia with an inability to gaze toward the side of the lesion. The ipsilateral eye is immobile in the horizontal plane and movement of the contralateral eye is restricted to abduction, which may be associated with nystagmus. The causes include pontine infarct, multiple sclerosis, and pontine hemorrhage.

B. Diplopia Testing. When the patient complains of diplopia, maneuvers to test eye movement should be used to determine its anatomic basis. The patient is asked to fix his or her vision on an object, such as a flashlight, in each of the six cardinal positions of gaze. With normal conjugate gaze, light from the flashlight falls at the same spot on both corneas; a lack of such congruency confirms that gaze is disconjugate. When the patient notes diplopia in a given direction of gaze, each eye should be covered in turn and the patient asked to report which of the two images disappears. The image displaced farther in the direction of gaze is always referable to the weak eye, because that image will not fall on the fovea. A variation of this procedure is the red glass test, in which one eye is covered with translucent red glass, plastic, or cellophane; this allows the eye responsible for each image to be identified.

C. Nystagmus. Nystagmus is rhythmic oscillation of the eyes. **Pendular nystagmus,** which usually has its onset in infancy, occurs with equal velocity in both directions. **Jerk nystagmus** is characterized by a slow phase of movement followed by a fast phase in the opposite direction; the direction of jerk nystagmus is specified by stating the direction of the fast phase (eg, leftward-beating nystagmus). Jerk nystagmus usually increases in amplitude with gaze in the direction of the fast phase.

Nystagmus, a normal component of both the optokinetic response and the response to caloric stimulation of reflex eye movements, can also occur at the extremes of voluntary gaze in normal subjects. In other settings, however, it is commonly due to anticonvulsant or sedative drugs or is a sign of disease in the peripheral vestibular apparatus, central vestibular pathways, or cerebellum.

To detect nystagmus, the eyes are observed in the primary position and in each of the cardinal positions of gaze. Nystagmus is described in terms of the

position of gaze in which it occurs, its direction and amplitude, precipitating factors such as changes in head position, and associated symptoms, such as vertigo.

Many forms of nystagmus and related ocular oscillations have been described, but two syndromes of acquired pathologic jerk nystagmus are by far the most common.

1. Gaze-evoked nystagmus. As its name implies, gaze-evoked nystagmus occurs when the patient attempts to gaze in one or more directions away from the primary position. The fast phase is in the direction of gaze. Nystagmus evoked by gaze in a single direction is a common sign of early or mild residual ocular palsy. Multidirectional gaze-evoked nystagmus is most often an adverse effect of anticonvulsant or sedative drugs, but it can also result from cerebellar or central vestibular dysfunction.

2. Vestibular nystagmus. Vestibular nystagmus increases with gaze toward the fast phase and is usually accompanied by vertigo when caused by a lesion of the peripheral vestibular apparatus. Vestibular nystagmus is characteristically unidirectional, horizontal, or horizontal and rotatory and associated with severe vertigo. In contrast, central vestibular nystagmus may be bidirectional and purely horizontal, vertical, or rotatory, and the accompanying vertigo is typically mild. Positional nystagmus – elicited by changes in head position – can occur with either peripheral or central vestibular lesions. The most helpful distinguishing features are the presence of hearing loss or tinnitus with peripheral lesions and of corticospinal tract or additional cranial nerve abnormalities with central lesions.

DISORDERS OF THE VISUAL SYSTEM

Common syndromes of monocular visual loss include two reversible and two irreversible disorders. Transient monocular blindness caused by optic nerve ischemia is sudden in onset and resolves rapidly. Subacute, painful, unilateral visual loss with partial resolution is associated with optic neuritis. Irreversible visual loss of sudden onset occurs in idiopathic ischemic optic neuropathy and in giant cell (temporal) arteritis.

1. TRANSIENT MONOCULAR BLINDNESS

This condition, sometimes called amaurosis fugax, is characterized by unilateral transient diminution or loss of vision that develops over seconds, remains maximal for 1-5 minutes, and resolves over 10-20 minutes. Although the cause of these episodes often remains uncertain, the presence of what appears to be embolic material in retinal arteries during episodes suggests that emboli are

the cause. The major site of origin of such emboli appears to be atherosclerotic lesions at the carotid bifurcation. Mitral valve prolapse and other cardiac sources of emboli can produce a similar syndrome. The risk for subsequent hemispheric infarction is increased (14% within 7 years) in patients with a history of transient monocular blindness but is only about one-half that in patients with hemispheric transient ischemic attacks (TIAs).

Diagnostic evaluation and treatment of patients with transient monocular blindness resemble that recommended for patients with hemispheric TIAs. Recent studies have shown that in patients with transient monocular blindness or TIAs and high-grade (>70%) stenosis of the carotid artery at angiography, the combination of aspirin plus surgical removal of thrombus (endarterectomy) is superior to aspirin alone.

2. OPTIC NEURITIS

Inflammation of the optic nerve produces the syndrome of optic neuritis, which can be idiopathic; it is caused by demyelination or (rarely) parameningeal, meningeal, or intraocular inflammation or is associated with viral infections or post-viral-infection syndromes. Unilateral impairment of visual acuity occurs over hours to days, becoming maximal within 1 week. The visual loss is associated with headache, globe tenderness, or eye pain; the last is typically exacerbated by eye movement.

On visual field testing, there is usually a central scotoma (blind spot) associated with decreased visual acuity. Examination of the fundus is normal in two-thirds of patients, since the inflammatory process is usually posterior to the optic disk (retrobulbar neuritis), but unilateral disk swelling may be seen. The pupils are equal in size but show a diminished reaction to illumination of the affected eye (relative afferent pupillary defect; discussed above). Visual acuity usually but not invariably improves over 2-3 weeks to normal. Intravenous methylprednisolone, 1 g/d for 3 days, followed by oral prednisone, 1 mg/kg/d for 11 days, has been shown to hasten recovery but does not alter the final outcome. Oral prednisone alone in lower doses was associated with a higher recurrence rate than occurred in patients treated with placebo. The frequency with which optic neuritis is the first sign of more widespread central nervous system demyelination (multiple sclerosis) remains uncertain and varies with the length of follow-up studies. Most prospective and retrospective series, however, report progression to definite multiple sclerosis in many of these patients (74% of women and 34% of men) over the subsequent 15 years. Rare causes of optic neuropathy include toxins (eg, methanol, ethambutol), neurosyphilis, and vitamin B_{12} deficiency.

3. ANTERIOR ISCHEMIC OPTIC NEUROPATHY (AION)

Idiopathic infarction of the anterior portion of the optic nerve is termed anterior ischemic optic neuropathy. Such visual loss is sudden in onset, usually painless, always monocular, and without premonitory ocular symptoms. Visual loss is usually maximal at onset and frequently subtotal, producing a field defect that is typically altitudinal (superior or inferior) in configuration; in one-third of cases the course is stuttering or progressive. Examination reveals ipsilateral disk swelling. In the absence of this finding, the diagnosis is tenuous, and other causes, such as a rapidly expanding intracranial mass or neoplastic meningitis, should be sought. Although ischemic optic neuropathy is often assumed to be atherosclerotic in origin, there is no consistent association with other risk factors for cerebrovascular disease, such as hypertension, diabetes, or atherosclerotic carotid artery disease. Patients with AION have a structurally smaller disc than nomal; 40% will go on to have the other eye affected within 2-4 years. Attempts at treatment have been uniformly unsuccessful. As disk swelling resolves, ophthalmoscopic evaluation shows optic atrophy.

4. GIANT CELL (TEMPORAL) ARTERITIS

Arteritic infarction of the anterior portion of the optic nerve is the most devastating complication of giant cell, or temporal, arteritis. This disorder is usually accompanied by systemic symptoms such as fever, malaise, night sweats, weight loss, and headache and often by polymyalgia rheumatica. Transient retinal ischemia, mimicking embolic events, may precede optic nerve infarction. The visual loss is sudden and often total. On examination, the optic disk appears swollen and pale. Immediate treatment with corticosteroids (methylprednisolone, 1000 mg/d intravenously, then prednisone, 60-80 mg/d orally) is urgently required to protect what vision remains. The prednisone may be gradually reduced over many months while monitoring the erythrocyte sedimentation rate.

Because giant cell arteritis is treatable, it is most important to distinguish it from anterior ischemic optic neuropathy as the cause of monocular visual loss. Patients with giant cell arteritis tend to be older (aged 70-80 years), and they may have premonitory symptoms. The most helpful differential features are the erythrocyte sedimentation rate, which is greater than 50 mm/h (Westergren) in most patients with giant cell arteritis, and the C-reactive protein.

5. PAPILLEDEMA

Papilledema is the passive bilateral disk swelling that is associated with increased intracranial pressure. Less common causes include congenital cyanotic heart disease and disorders associated with increased CSF protein content, in-

cluding spinal cord tumor and idiopathic inflammatory polyneuropathy (Guillain-Barre syndrome).

The speed with which papilledema develops is dictated by the underlying cause. When intracranial pressure increases suddenly, as in subarachnoid or intracerebral hemorrhage, disk swelling may be seen within hours, but it most often evolves over days. Papilledema may require 2-3 months to resolve following restoration of normal intracranial pressure. Associated nonspecific symptoms of raised intracranial pressure include headache, nausea, vomiting, and diplopia from abducens nerve palsy. Funduscopic examination reveals (in order of onset) blurring of the nerve fiber layer, absence of venous pulsations (signifying intracranial pressure greater than approximately 200 mm Hg), hemorrhages in the nerve fiber layer, elevation of the disk surface with blurring of the margins, and disk hyperemia.

Papilledema requires urgent evaluation to search for an intracranial mass and to exclude papillitis from syphilis, carcinoma, or sarcoidosis, which may produce a similar ophthalmoscopic appearance. In the history and examination, attention should be directed at symptoms and signs of intracranial masses, such as hemiparesis, hemianopia or seizures, and signs of meningeal irritation.

If an intracranial mass lesion and some other disorders are ruled out by the history, examination, and CT scanning or MRI; if inflammatory meningeal processes are excluded by CSF examination; and if CSF pressure is elevated, a diagnosis of pseudotumor cerebri is established by exclusion. The idiopathic form, which is the most common, occurs most often in obese women during the childbearing years. Although this disorder is usually self-limited, prolonged elevation of intracranial pressure can lead to permanent visual loss.

6. CHIASMAL LESIONS

The major lesions that produce visual impairment at the level of the optic chiasm are tumors, especially those of pituitary origin. Other causes include trauma, demyelinating disease, and expanding berry aneurysms. The classic pattern of visual deficit caused by lesions of the optic chiasm is bitemporal hemianopia. Chiasmal visual loss is gradual in onset, and the resulting impairment in depth perception or in the lateral visual fields may not be noted for some time. Associated involvement of the oculomotor, trochlear, trigeminal, or abducens nerve suggests tumor expansion laterally into the cavernous sinus. Nonophthalmologic manifestations of pituitary tumors include headache, acromegaly, amenorrhea, galactorrhea, and Cushing's syndrome.

Headache, endocrine abnormalities, and occasionally blurred or double vision may occur in patients with an enlarged sella turcica (shown on radiographic examination) but in whom neither tumor nor increased intracranial pressure is found. This empty sella syndrome is most common in women and occurs

mainly between the fourth and seventh decades of life. Treatment is symptomatic.

7. RETROCHIASMAL LESIONS

Optic Tract & Lateral Geniculate Body

Lesions of the optic tract and lateral geniculate body are usually due to infarction. The resulting visual field abnormality is typically a noncongruous homonymous hemianopia; ie, the field defect is not the same in the two eyes. Associated hemisensory loss may occur with thalamic lesions.

Optic Radiations

Lesions of the optic radiations produce field deficits that are congruous and homonymous (bilaterally symmetric). Visual acuity is normal in the unaffected portion of the field. With lesions in the temporal lobe, where tumors are the most common cause, the field deficit is denser superiorly than inferiorly, resulting in a superior quadrantanopia (pie in the sky deficit).

Lesions affecting the optic radiations in the parietal lobe may be due to tumor or vascular disease and are usually associated with contralateral weakness and sensory loss. A gaze preference is common, with the eyes conjugately deviated to the side of the parietal lesion. The visual field abnormality is either complete homonymous hemianopia or inferior quadrantanopia. The optokinetic response to a visual stimulus moved toward the side of the lesion is impaired, which is not the case with pure temporal or occipital lobe lesions.

Occipital Cortex

Lesions in the occipital cortex usually produce homonymous hemianopias affecting the contralateral visual field. The patient may be unaware of the visual deficit. Since the region of the occipital cortex in which the macula is represented is often supplied by branches of both the posterior and middle cerebral arteries, visual field abnormalities caused by vascular lesions in the occipital lobe may show sparing of macular vision. It has also been suggested that in some cases, macular sparing may result from bilateral cortical representation of the macular region of the visual field.

The most common cause of visual impairment in the occipital lobe is infarction in the posterior cerebral artery territory (90% of cases). Occipital lobe arteriovenous malformations (AVMs), vertebral angiography, and watershed infarction following cardiac arrest are less common causes. Additional symptoms and signs of basilar artery ischemia may occur. Tumors and occipital lobe AVMs are often associated with unformed visual hallucinations that are typically unilateral, stationary or moving, and often brief or flickering; they can be colored or not colored.

Bilateral occipital lobe involvement produces cortical blindness. Pupillary reactions are normal, and bilateral macular sparing may preserve central (tunnel)

vision. With more extensive lesions, denial of blindness may occur (Anton's syndrome).

DISORDERS OF OCULAR MOTILITY

GAZE PALSY

Lesions in the cortex or brainstem above the level of the oculomotor nuclei may impair conjugate (yoked) movement of the eyes, producing gaze disorders.

Hemispheric Lesions

Acutely, hemispheric lesions produce tonic deviation of both eyes toward the side of the lesion and away from the side of the hemiparesis. This gaze deviation lasts for up to several days in alert patients-somewhat longer in comatose patients. Seizure discharges involving the frontal gaze centers can also produce gaze deviation by driving the eyes away from the discharging focus. When the ipsilateral motor cortex is also involved, producing focal motor seizures, the patient gazes toward the side of the motor activity.

Midbrain Lesions

Lesions of the dorsal midbrain affect the center responsible for voluntary upward gaze and may therefore produce upgaze paralysis. In addition, all or some of the features of Parinaud's syndrome may occur. These include preserved reflex vertical eye movements with the doll's head maneuver or Bell's phenomenon (elevation of the eye with eyelid closure), nystagmus (especially on downward gaze and typically associated with retraction of the eyes), paralysis of accommodation, midposition pupils, and light-near dissociation.

Pontine Lesions

Brainstem lesions at the level of the pontine gaze centers produce disorders of conjugate horizontal gaze. Gaze palsies from pontine involvement (unlike those from hemispheric lesions) cause eye deviation toward-rather than away from-the side of the hemiparesis. This occurs because, at this level of the brainstem, the corticobulbar pathways that regulate gaze have decussated but the descending motor pathways have not. Brainstem gaze pareses are characteristically far more resistant to attempts to move the eyes (via the doll's eye maneuver or caloric stimulation) than are supratentorial gaze pareses and are commonly associated with abducens nerve dysfunction because of the involvement of the abducens nerve nucleus.

INTERNUCLEAR OPHTHALMOPLEGIA

Internuclear ophthalmoplegia results from lesions of the medial longitudinal fasciculus between the midpons and the oculomotor nerve nucleus that disconnect the abducens nerve nucleus from the contralateral oculomotor nucleus.

The site of the internuclear ophthalmoplegia is named according to the side on which oculomotor nerve function is impaired. There is a characteristic abnormality consisting of disconjugate gaze with impaired adduction and nystagmus of the abducting eye. Such a finding strongly supports a diagnosis of intrinsic brainstem disease. The most common cause, especially in young adults or in patients with bilateral involvement, is multiple sclerosis. In older patients and those with unilateral involvement, vascular disease is likely. These two diagnoses encompass 80% or more of all cases in reported series. Rarer causes include brainstem encephalitis, intrinsic brainstem tumors, syringobulbia, sedative drug intoxication, and Wernicke's encephalopathy. Because the oculomotor abnormalities of myasthenia gravis can closely mimic a lesion of the medial longitudinal fasciculus, myasthenia must be ruled out in patients with isolated internuclear ophthalmoplegia.

OCULOMOTOR (III) NERVE LESIONS

Brainstem

Within the brainstem, associated neurologic signs permit localization of the lesion; associated contralateral hemiplegia (Weber's syndrome) and contralateral ataxia (Benedikt's syndrome) are the most common vascular syndromes.

Subarachnoid Space

As the oculomotor nerve exits the brainstem in the interpeduncular space, it is susceptible to injury from trauma and from aneurysms of the posterior communicating artery. The latter often cause acute oculomotor palsy from aneurysmal expansion with a characteristic impairment of the pupillary light reflex.

Cavernous Sinus

In the cavernous sinus the oculomotor nerve is usually involved along with the trochlear and abducens nerves and the first and sometimes the second division of the trigeminal nerve. Homer's syndrome may occur. Oculomotor nerve lesions in the cavernous sinus tend to produce partial deficits that mayor may not spare the pupil.

Orbit

Unlike cavernous sinus lesions, orbital lesions that affect the oculomotor nerve are often associated with optic nerve involvement and exophthalmos; however, disorders of the orbit and cavernous sinus may be clinically indistinguishable except by CT scanning or MRI.

TROCHLEAR (IV) NERVE LESIONS

Head trauma, often minor, is the most common cause of an isolated trochlear nerve palsy. While trochlear palsies in middle-aged and elderly patients are also frequently attributed to vascular disease or diabetes, they often occur without obvious cause. For patients with isolated trochlear nerve palsies

without a history of trauma, in whom diabetes, myasthenia, thyroid disease, and orbital mass lesions have been excluded, observation is the appropriate clinical approach.

ABDUCENS (VI) NERVE LESIONS

Patients with abducens nerve lesions complain of horizontal diplopia due to weakness of the lateral rectus muscle. Lateral rectus palsies can occur as a result of disorders of either the muscle itself or the abducens nerve, and each of these possibilities should be investigated in turn. In elderly patients, abducens nerve involvement is most often idiopathic or caused by vascular disease or diabetes, but the erythrocyte sedimentation rate should be determined to exclude a rare presentation of giant cell arteritis. Radiographic investigation of the base of the skull is indicated to exclude nasopharyngeal carcinoma or other tumors. In painless abducens palsy-when the above studies are normal, other systemic and neurologic symptoms are absent, and intracranial pressure is not elevated-patients can be followed conservatively. A trial of prednisone (60 mg/d orally for 5 days) may produce dramatic relief in painful abducens nerve palsy, giving support to a tentative diagnosis of idiopathic inflammation of the superior orbital fissure (superior orbital fissure syndrome) or cavernous sinus (Tolosa-Hunt syndrome). Persistent pain despite treatment with steroids should prompt investigation of the cavernous sinus by CT scanning or MRI, followed, in some cases, by angiography.

DIABETIC OPHTHALMOPLEGIAS

An isolated oculomotor, trochlear, or abducens nerve lesion may occur in patients with diabetes mellitus, and noninvasive imaging procedures (CT scanning or MRI) reveal no abnormality. Such oculomotor nerve lesions are characterized by pupillary sparing with or without pain. Pain, when present, may be severe enough to suggest aneurysmal expansion as a likely diagnosis. The lack of pupillary involvement is commonly attributed to infarction of the central portion of the nerve with sparing of the more peripherally situated fibers that mediate pupillary constriction. Pupil-sparing oculomotor palsies can also be seen occasionally, however, with compressive, infiltrative, or inflammatory lesions of the oculomotor nerve or with infarcts, hemorrhages, or tumors that affect the oculomotor nucleus or fascicle within the midbrain.

In known diabetics, painful ophthalmoplegia with exophthalmos and metabolic acidosis requires urgent attention to determine the possibility of fungal infection in the paranasal sinus, orbit, or cavernous sinus by mucormycosis. The diagnosis is usually made by biopsy of the nasal mucosa. Failure to make a prompt diagnosis and to institute treatment at once with amphotericin B and surgical debridement of necrotic tissue may lead to a fatal outcome.

PAINFUL OPHTHALMOPLEGIAS

Dysfunction of one or more of the ocular motor nerves with accompanying pain may be produced by lesions located anywhere from the posterior fossa to the orbit. The evaluation should consist of careful documentation of the clinical course, inspection and palpation of the globe for proptosis (localizing the process to the orbit or anterior cavernous sinus), auscultation over the globe to detect a bruit (which would strongly support a diagnosis of carotid artery-cavernous sinus fistula or another vascular anomaly), and evaluation for diabetes. Useful laboratory studies include an orbital CT scan or MRI, carotid arteriography, and orbital venography.

Therapy for these disorders is dictated by the specific diagnosis. Idiopathic inflammation of the orbit (orbital pseudotumor) or cavernous sinus (Tolosa Hunt syndrome) responds dramatically to corticosteroids (prednisone, 60-100 mg/d orally). However, the pain and ocular signs of some neoplasms may also improve transiently during corticosteroid therapy so that a specific etiologic diagnosis may depend on biopsy.

MYASTHENIA GRAVIS

Myasthenia eventually involves the ocular muscles in approximately 90% of patients; more than 60% present with ocular involvement. The syndrome is painless; pupillary responses are always normal, and there are no sensory abnormalities. The diagnosis is confirmed by a positive response to intravenous edrophonium (Tensilon).

OCULAR MYOPATHIES

Ocular myopathies are painless syndromes that spare pupillary function and are usually bilateral. The most common is the myopathy of hyperthyroidism, a common cause of double vision beginning in midlife or later. Note that many patients are otherwise clinically euthyroid at the time of diagnosis. Double vision on attempted elevation of the globe is the most common symptom, but in mild cases there is lid retraction during staring or lid lag during rapid up-and-down movements of the eye. Exophthalmos is a characteristic finding, especially in advanced cases. The diagnosis can be confirmed by the forced duction test, which detects mechanical resistance to forced movement of the anesthetized globe in the orbit. This restrictive ocular myopathy is usually self-limited. The patient should be referred for testing of thyroid function and treated for hyperthyroidism as appropriate.

The progressive external ophthalmoplegias are a group of syndromes characterized by slowly progressive, symmetric impairment of ocular movement

that cannot be overcome by caloric stimulation. Pupillary function is spared, and there is no pain; ptosis may be prominent. This clinical picture can be produced by ocular or oculopharyngeal muscular dystrophy. Progressive external ophthalmoplegia associated with myotonic contraction on percussion of muscle groups (classically, the thenar group in the palm) suggests the diagnosis of myotonic dystrophy. In Kearns-Sayre-Daroff syndrome, which has been associated with deletions in muscle mitochondrial DNA, progressive external ophthalmoplegia is accompanied by pigmentary degeneration of the retina, cardiac conduction defects, cerebellar ataxia, and elevated CSF protein. The muscle biopsy shows ragged red fibers that reflect the presence of abnormal mitochondria. Disorders that simulate progressive external ophthalmoplegia include progressive supranuclear palsy and Parkinson's disease, but in these conditions the impairment of (usually vertical) eye movements can be overcome by oculocephalic or caloric stimulation.

TRIGEMINAL NERVE (V)

FUNCTIONAL ANATOMY

The trigeminal nerve contains both sensory (afferent) and motor (efferent) fibres. Sensory information is conveyed from the skin of the face and forehead, from the mucous membranes of the nasal sinuses and oral cavities, from the teeth, and from the dura of the anterior and middle cranial fossae. Efferent fibres innervate the masseter, temporalis, and pterygoid muscles (the muscles of mastication). Whereas the organization of the motor pathways is relatively straighforward, the sensory system is complex, with three major peripheral branches (each with several smaller branches), and two central pathways each subserving different sensory modalities. The peripheral distribution will be discussed first followed by a description of the central connections.

Peripheral sensory pathways

The cell bodies of the afferent fibres lie in the trigeminal ganglion (also known as the Gasserian or semilunar ganglion) which sits in a dural cavity (Meckel's cave) near the tip of the petrous apex bone. The peripheral processes of these unipolar ganglion cells give rise to the three main divisions of the trigeminal nerve: the ophthalmic, maxillary, and mandibular branches, often conveniently referred to as V1, V2 and V3. The central processes form the sensory root which enters the pons on its lateral aspect.

The ophthalmic nerve passes forwards in the lateral wall of the cavernous sinus, where it lies close to the third, fourth, and sixth cranial nerves, and enters the orbit through the superior orbital fissure. Branches of the nerve supply sensation to the scalp, forehead and nose, to the mucous membrane of the frontal sinus and upper part of the nasal cavity, and to the eye (conjunctiva and cornea), the latter providing the afferent limb of the corneal reflex. The area of cutaneous distribution is clearly defined but often misunderstood. Posteriorly, the nerve supplies the scalp as far back as the lambdoidal suture. Non-organic sensory loss over the face and forehead often extends only to the hairline, but care must be taken in interpretation because such apparently non-anatomical distribution of sensory loss may be seen in organic disease. The lateral extent of the cutaneous distribution and the boundaries with the areas of supply of the maxillary and mandibular divisions.

The maxillary nerve passes through the inferior part of the cavernous sinus and leaves the skull through the foramen rotundum. A major branch, the infraorbital nerve, enters the orbit through the inferior orbital fissure and exits through the infraorbital foramen. The nerve also supplies the mucous membrane

of the upper lip, hard palate, and anterior part of the soft palate, the mucous membrane of the maxillary sinus and of the lower nasal cavity, and the teeth of the upper jaw.

The mandibular nerve fuses with the motor root and leaves the skull through the foramen ovale. The angle of the jaw is not supplied by the mandibular nerve, but in non-organic facial sensory loss this area is often affected. As noted for ophthalmic sensory loss, caution must be taken in interpreting this sign. The area of sensory supply includes part of the pinna, external auditory meat us, and tympanic membrane. The nerve also supplies the mucous membrane of the cheek, floor of the mouth and anterior two-thirds of the tongue, and the teeth of the lower jaw. The lingual branch carries taste fibres from the anterior two-thirds of the tongue, which then join the facial nerve via the chorda tympani.

Peripheral motor pathways

The motor fibres emerging from the pons pass under the trigeminal ganglion and fuse with sensory fibres to form the mandibular nerve, which leaves the skull through the foramen ovale. They innervate the temporalis, masseter, and medial and lateral pterygoid muscles. Other muscles are supplied by the mandibular nerve, but they cannot be tested at the bedside and their involvement in isolation is not associated with specific clinical features.

Central connections

The sensory root, formed by the central processes of the trigeminal ganglion cells, enters the lateral pons and divides into short ascending and long descending branches. The short ascending fibres terminate in the principal sensory nucleus of the trigeminal nerve, which lies in the substantia gelatinosa of the lateral tegmentum of the upper pons. These fibres subserve tactile and pressure sensation (in clinical practice, lesions impair light-touch sensation and the corneal reflex). The long descending fibres form the spinal trigeminal tract, which reaches down as far as the upper cervical spinal cord (C2 level). As the tract descends, the fibres gradually terminate in the medially placed substantia gelatinosa, forming the spinal trigeminal nucleus which therefore can also be seen to extend from the pons down to the upper cervical cord. This pathway subserves pain and thermal sensation (in clinical practice, lesions impair pinprick and temperature sensation). There is a specific but complex topographical arrangement of fibres within the trigeminal tract; fibres from the ophthalmic division lie most ventrally, and those from the mandibular division most dorsally.

The secondary trigeminal pathways arise from the primary sensory nucleus and from the spinal trigeminal nucleus. Crossed and uncrossed fibres are important in various reflex pathways, discussed below, but the major sensory pathways involve crossed fibres. The secondary fibres arising from the principal sensory nucleus cross the midline in the pons and ascend as the quintothalamic tract, in close association with the medial lemniscus. Secondary fibres arising from the long spinal trigeminal nucleus cross the midline raphe and ascend in

association with the medial lemniscus. Secondary trigeminal pathways, from both the principal sensory nucleus and the spinal trigeminal nucleus, terminate in the thalamus.

Trigeminal reflexes

Secondary crossed and uncrossed fibres from the two trigeminal nuclei are involved in several reflex pathways, including lacrimation, sneezing, and vomiting. In clinical practice the most important are the corneal reflex and the jaw jerk.

Stimulation of the cornea sends afferent impulses via the ophthalmic division to the trigeminal nucleus. Secondary fibres project bilaterally to the facial nuclei which, with the facial nerves, complete the reflex arc. Unilateral corneal sensation evokes bilateral blinking. In the presence of a facial-nerve palsy, ipsilateral corneal stimulation will cause contralateral blinking. Corneal stimulation on the side of an ophthalmic nerve lesion will produce no response, but contralateral corneal stimulation will produce bilateral blinking.

The jaw jerk is a monosynaptic reflex. Jaw tapping invokes bilateral contraction of the masseter and temporalis muscles. The reflex is not noticeably affected by a unilateral upper or lower motor neuron lesion of the trigeminal nerve, but is exaggerated in the presence of bilateral upper motor neuron lesions.

LESIONS OF THE TRIGEMINAL NERVE

Trigeminal nerve function may be affected by supranuclear (upper motor neuron), nuclear, or peripheral lesions.

Supranuclear lesions

The motor nuclei receive bilateral supranuclear (corticobulbar) innervation. A unilateral upper motor neuron lesion (e.g. a hemispheric stroke) causes no clinically discernible weakness of the trigeminal nerve-innervated muscles. Bilateral upper motor neuron lesions (e.g. bilateral hemispheric strokes, occurring simultaneously or consecutively, or an upper brainstem lesion affecting both corticobulbar pathways) result in a pseudobulbar palsy with dysarthria, dysphagia, and a brisk jaw jerk.

Nuclear lesions

Lesions involving the motor nucleus in the pons will cause ipsilateral weakness and wasting of the muscles of mastication. Masseter and temporalis can be seen and felt to be wasted, on jaw closure, and on jaw opening the jaw will deviate to the affected side because of weakness of the pterygoid muscles.

Isolated involvement of the pontine primary sensory nucleus would be expected to produce ipsilateral loss of facial lighttouch sensation, with preservation of pinprick sensation, but in practice lesions invariably also involve de-

scending fibres and both sensory modalities are impaired. Lesions in this area affecting trigeminal motor and sensory function also frequently cause contralateral hemiplegia and spinothalamic sensory loss. Common pathologies include vascular disease, demyelination, and tumour. Rarer causes are a variety of vascular malformations and (very rare) syringobulbia.

Lesions in the medulla and upper cervical cord may affect the spinal trigeminal tract and nucleus, causing ipsilateral loss of facial pain (pinprick) and temperature sensation, with preservation of light-touch and the corneal reflex. By far the most common cause is infarction of the lateral medulla secondary to occlusion of the vertebral artery or the posterior inferior cerebellar artery (the lateral medullary syndrome of Wall enberg). Further symptoms include hiccoughs, dizziness, dysarthria, and dysphagia. Ipsilateral signs, in addition to the facial sensory loss, include Horner's syndrome, palatal and vocal cord paresis, and cerebellar ataxia. Contralaterally there is limb and trunk spinothalamic (pinprick and temperature) sensory loss.

In syringomyelia a central cord lesion (a syrinx or cavity) gradually extends upwards from the cervical spinal cord into the medulla (when it is referred to as syringobulbia) and possibly as far as the pons. Spinal cord tumours may behave in the same fashion. In these situations there is bilateral involvement of the trigeminal tract and nuclei and, due to the topographic organization of nerve fibres, a particular pattern of facial sensory loss (to pinprick and temperature) evolves, which has been likened to an onion-skin or the wearing of a balaclava helmet. Thus, the sensory loss gradually progresses forwards and medially towards the nose.

Peripheral lesions

Numerous pathologies can affect the intracranial parts of the trigeminal nerve complex (the motor and sensory roots, trigeminal ganglion, and the three major nerve divisions). These include tumours (metastases, carcinomatous meningitis, acoustic neuromas, trigeminal neuromas, meningiomas, nasopharyngeal carcinoma), infections (viral, acute and chronic meningitis, abscesses, osteitis), Paget's disease, trauma, aneurysms, and granulomatous processes. Depending upon the site of the lesion, other cranial nerves may be involved and particular syndromes can be identified.

A lesion affecting both the sympathetic nerve fibres around the internal carotid artery and the trigeminal ganglion may produce a Horner's syndrome (without anhydrosis as sudomotor fibres travel along the external carotid artery) and trigeminal nerve involvement (either with pain alone or with a demonstrable sensorimotor neuropathy). This combination is referred to as Raeder's paratrigeminal syndrome, and causes include carotid aneurysm, infection, tumours, and trauma. Such lesions may involve the optic nerve and cranial nerves III, IV, and VI in the parasellar region.

Peripheral branches of the three main nerves may be damaged by blunt or penetrating, or surgical, trauma, resulting in areas of sensory disturbance, sometimes accompanied by continuous or neuralgic pain. Those most commonly affected are the supraorbital, infraorbital, and inferior alveolar nerves. The rather specific numb cheek and chin syndromes are discussed below.

Trigeminal neuralgia is the most frequently encountered disorder of the trigeminal nerve. It may be symptomatic of an underlying structural disorder affecting the nerve, but in the majority of patients no specific cause is identified. It is more common in the second half of life, cases in younger people more often being symptomatic, is slightly more frequent in women.

EXAMINATION

Facial Sensation

Simultaneously touch both sides of the forehead, then the cheek, and then the jaw and ask if they feel the same. Check for temperature perception in the same sequence, using the cool surface of a tuning fork or other appropriate stimulus. The stimulus will be perceived as warmer on the side of impaired sensation.

Corneal Reflex

Sweep a wisp of cotton lightly across the lateral surface of the eye (out of the direct visual field) from sclera to cornea. As soon as the stimulus reaches the sensitive cornea, the patient will wince and blink vigorously if nerves V and VII are both intact. Compare the sides for symmetry.

Motor V Testing

Observe the symmetry of opening and closing of the mouth; the jaw will fall faster and farther on the side of the lesion, so that the face looks askew. For more subtle weakness, ask the patient to clench the teeth and then attempt to force jaw opening or lateral jaw displacement. Normal strength cannot be overcome.

FACIAL NERVE (VII)

FUNCTIONAL ANATOMY

The facial nerve has two roots. The larger contains the motor nerve fibres which supply the ipsilateral facial muscles. The smaller root, the intermediate nerve, contains fibres conveying taste sensation from the anterior two-thirds of the tongue, cutaneous sensory fibres from the posterior part of the ear, and preganglionic parasympathetic fibres that innervate the lacrimal and submandibular glands.

Motor pathways

The facial-nerve motor nucleus lies in the ventrolateral tegmentum of the pons. The efferent fibres arising from the nucleus sweep dorsomedially, to the floor of the fourth ventricle, loop sharply around the sixth nerve nucleus, and then pass ventrolaterally to emerge from the lateral border of the caudal pons, at the cerebellopontine angle. The facial nerve is medial to the eighth nerve and between the two lies the intermediate nerve. These three nerves pass through the internal acoustic meatus and then the facial nerve and intermediate nerve enter the facial canal. In the facial canal, on the medial side of the middle ear, the facial nerve turns sharply (the genu of the facial nerve), moving posteriorly and inferiorly, gives off a branch to the stapedius muscle, and exits from the skull through the stylomastoid foramen.

After leaving the stylomastoid foramen the facial nerve sends branches to the stylohyoid muscle and to the posterior belly of the digastric, and then passes through the parotid gland, dividing into several branches which supply platysma and all of the muscles of facial expression, excluding levator palpebrae superioris (which is supplied by the oculomotor nerve-thus, facial-nerve lesions do not cause ptosis).

Corticobulbar pathways

The facial nucleus is composed of a number of distinct cell groups, each innervating specific facial muscles. Those supplying the upper facial muscles receive bilateral supranuclear (corticobulbar) innervation, whereas those supplying the lower facial muscles receive mainly crossed fibres from the contralateral hemisphere. In addition to direct corticobulbar fibres, there are several indirect pathways between the cortex and facial nuclei, involving the thalamus and reticular formation.

Sensory pathways

In the facial canal there is an expansion of the facial nerve as it makes its sharp backwards turn, at the genu. This expansion is the geniculate ganglion and

is formed by the cell bodies of the nerves that give rise to the two sensory components of the facial nerve.

Special visceral afferent fibres convey taste sensation from the anterior two-thirds of the tongue. From the tongue these fibres travel first in the lingual nerve, and then in the chorda tympani which enters the skull, crosses the tympanic cavity, and joins the facial nerve in the facial canal. From the geniculate ganglion, the central connections pass via the intermediate nerve and terminate in the nucleus solitarius in the medulla.

Cutaneous nerve fibres arise from a small area, which includes the posterior part of the external auditory meatus and the skin behind the ear and in front of the mastoid. They enter the facial canal just proximal to the stylomastoid foramen. From the cell bodies in the geniculate ganglion the fibres pass centrally in the intermediate nerve and terminate in the spinal trigeminal tract. Sensory loss is not a clinically detectable feature of facial-nerve lesions, presumably because of overlap from adjacent cutaneous nerve territories, but the presence of this sensory pathway probably explains the symptom of pain in the mastoid region which is so common in patients with Bell's palsy.

Autonomic pathways

Preganglionic parasympathetic fibres arise from the superior salivary nucleus, in the dorsolateral reticular formation. They travel in the intermediate nerve and at the genu of the facial nerve divide into two groups. One group passes with the greater superficial petrosal nerve to the pterygopalatine ganglion. Postganglionic fibres innervate the lacrimal gland and mucous membrane of the nose and mouth. The other group of fibres travels in the chorda tympani and terminates in the submandibular ganglion. Postganglionic fibres innervate the submandibular and sublingual salivary glands.

Facial-nerve reflexes

In clinical practice the corneal reflex and, to a lesser extent, the glabellar tap reflex, are of value. The glabellar tap reflex is polysynaptic and comprises tapping the forehead over the bridge of the nose and observing contraction of orbicularis oculi (i.e. blinking) bilaterally. After several taps there is habituation and blinking stops. In early childhood and in Parkinsonian syndromes there is failure of habituation and blinking continues in time with the tapping.

Other reflexes include the naso-lacrimal reflex (lacrimation in response to stimulation of the nasal mucosa), naso-mental reflex (tapping the side of the nose causes elevation of the upper lip), and the stapedius reflex (contraction of stapedius in response to a loud noise). These and other similar reflexes are of little importance at the bedside but some, such as the stapedial reflex, may be studied in the laboratory and can help with localization of facial-nerve lesions.

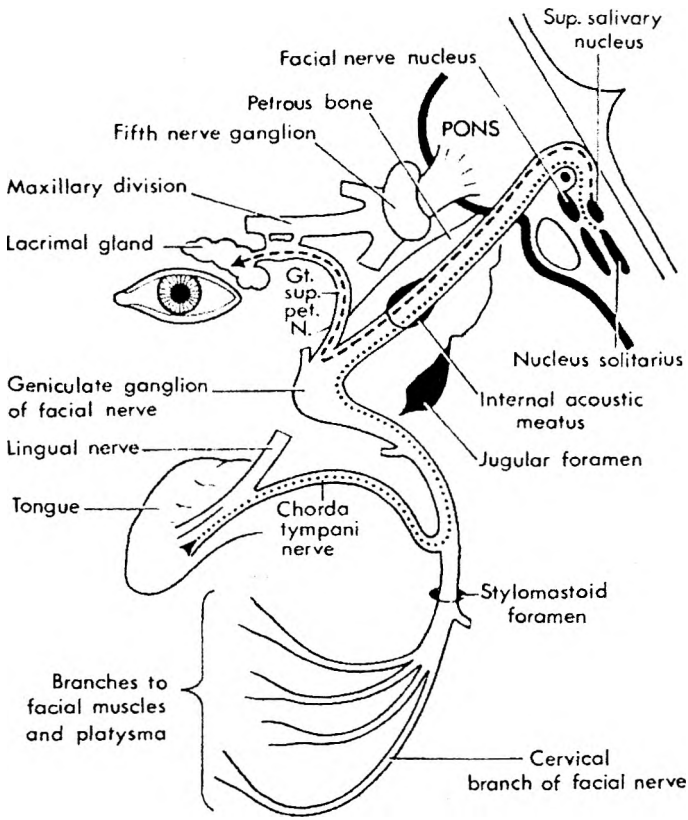


Fig 11. The facial nerve. lesions involving the facial-nerve trunk above the geniculate ganglion will cause loss of lacrimation (greater petrosal nerve) and loss of taste in the anterior two-thirds of the tongue (chorda tympani nerve), as well as paralysis of both upper and lower facial muscles. lesions between the geniculate ganglion and the point where the chorda tympani nerve leaves the facial nerve (6 mm above the stylomastoid foramen), will cause loss of taste sensation in the anterior two-thirds of the tongue, as well as paralysis of the facial muscles, but lacrimation will still be present. lesions below the point where the chorda tympani nerve leaves the facial nerve will cause paralysis of the facial muscles, but both taste and lacrimation will be present. (From Brain's Diseases of the Nervous System, 2001)

LESIONS OF THE FACIAL NERVE

Lesions of the facial nerve, its nucleus or supranuclear pathways, may produce facial muscle weakness; but only peripheral lesions, affecting the facial nerve itself, affect taste sensation and autonomic function. As noted above, numbness is not an expected finding in facial-nerve lesions, although symptomatic complaints of sensory disturbance are common in Bell's palsy.

Supranuclear lesions

The upper facial muscles have almost equal bilateral cortical representation, whereas the lower facial muscles receive mainly crossed fibres from the contralateral hemisphere. Thus, a unilateral upper motor neuron lesion causes contralateral facial weakness, with the lower part of the face being more affected than the upper (NB it is relative rather than absolute sparing of the upper facial muscles). As noted above, there is more than one pathway of supranuclear innervation and, depending upon the site of the lesion, spontaneous emotional movements may be more affected than voluntary movements, and vice versa.

Nuclear and peripheral lesions

A lesion of the nucleus or facial nerve generally causes equal weakness of all ipsilateral facial muscles and the clinical features are exemplified by Bell's palsy. Occasionally, partial lesions of the nucleus or nerve may selectively affect the lower facial muscles, thus mimicking the appearance seen with an upper motor neuron lesion.

Considering the origins and sites of union with the facial nerve of the greater superficial petrosal nerve, the nerve to stapedius and the chorda tympani, the presence of impaired lacrimation, hyperacusis or an impaired stapedial reflex, or altered taste sensation can help in localizing the site of a facial-nerve lesion. The absence of such features is not of localizing value.

The facial nucleus may be affected by pontine lesions, and the nerve by lesions in the cerebellopontine angle, within the petrous temporal bone and outside the skull.

Pontine lesions

These rarely affect the facial nucleus or nerve fibres in isolation, and associated features include ipsilateral lateral rectus or conjugate gaze palsy, trigeminal motor and sensory involvement, and contralateral hemiparesis and hemisensory loss. Common pathologies include vascular lesions, multiple sclerosis, and tumours, less common disorders being brainstem encephalitis, syringobulbia, and poliomyelitis. Bilateral facial paralysis due to agenesis of the facial nuclei (Mobius' syndrome) is a rare disorder that may be associated with other cranial nerve lesions and dysmorphic features.

Cerebellopontine angle lesion

The most common lesions at this site, which affect the facial nerve, intermediate nerve, and eighth nerve, are acoustic neuromas and meningiomas. Less common lesions include secondary tumours, nasopharyngeal carcinoma, developmental tumours, cholesteatomas, and any basal meningitic process (e.g. sarcoid).

Petrous temporal bone lesions

In the facial canal the nerve may be affected by infection spreading from the middle ear or mastoid, or by surgical procedures in that area. Inflammation and swelling of the facial nerve in the facial canal and at the stylomastoid foramen is presumed to be present in Bell's palsy. In the Ramsay Hunt syndrome swelling of the geniculate ganglion due to reactivation of latent herpes zoster infection may compress the motor fibres, or there may be direct infection of the motor nerve. The resultant facial palsy is accompanied by a rash, typically seen in the external auditory meatus, although it is often more extensive than this and involves the trigeminal distribution (e.g. the anterior pillar of the fauces) and cervical dermatomes. There is often pain around the ear.

Lesions outside the skull

Benign and malignant lesions of the parotid gland may involve some or all of the branches of the facial nerve.

Bilateral facial palsy

Bilateral, as well as unilateral, lower motor neuron facial weakness may be seen in Guillain-Barre syndrome, sarcoidosis (due to basal meningeal or parotid involvement), Lyme disease (often accompanied by facial rash and induration), HIV infection (at seroconversion), and Melkersson's syndrome. In the latter disorder, recurrent episodes of unilateral or bilateral facial swelling and facial palsy are associated with a deeply furrowed tongue.

EXAMINATION

A central "supranuclear" lesion, such as a hemispheric stroke, will preserve forehead wrinkling and cause only mild weakness of eye closure, while the lower face is more severely involved. If there is a peripherallesion of the cranial nerve (or nucleus), the entire hemiface will be flaccid and the eyelids will gape open.

Some cranial neuropathies or neuromuscular diseases cause bilateral facial weakness, and in such cases the usual criterion of facial asymmetry as a marker of weakness will not apply.

Facial Symmetry

Observe the patient's face for symmetry of the palpebral fissures and nasolabial folds at rest. Ask the patient to wrinkle the forehead, then to squeeze the eyes tightly shut (looking for asymmetry in the extent to which the eyelashes protrude), then to smile or snarl, saying, "Show me your teeth."

Bilateral Facial Weakness

Ask the patient to squeeze the eyes tightly shut, then press the lips tightly together, then puff air into the checks. If strength is normal, one should not be able to pry the eyelids open, force the lips apart, or forcibly expel air from the mouth.

VESTIBULOCOCHLEAR NERVE (VIII)

Disturbances of the eighth or vestibulocochlear cranial nerve and its central connections lead to various combinations of deafness, vertigo, and imbalance. The cochlear division of the nerve supplies the cochlea and is concerned with hearing, whereas the vestibular division supplies the semicircular canals, the utricle, and saccule, and is concerned in postural and equilibratory functions.

Equilibrium is the ability to maintain orientation of the body and its parts in relation to external space. It depends upon continuous visual, labyrinthine, and proprioceptive input and its integration in the brainstem and cerebellum.

Disorders of equilibrium result from diseases that affect central or peripheral vestibular pathways, the cerebellum, or the sensory pathways involved in proprioception. Such disorders usually present with vertigo and ataxia.

VERTIGO

Vertigo is the illusion of movement of the body or the environment. It is often associated with other symptoms, such as impulsion (a sensation that the body is being hurled or pulled in space), oscillopsia (a visual illusion of moving back and forth), nausea, vomiting, or gait ataxia.

Distinction between Vertigo & Other Symptoms

Vertigo must be distinguished from non vertiginous dizziness, which includes sensations of light-headedness, faintness, or giddiness not associated with an illusion of movement. In contrast to vertigo, these sensations are produced by conditions that impair the brain's supply of blood, oxygen, or glucose - eg, excessive vagal stimulation, orthostatic hypotension, cardiac arrhythmias, myocardial ischemia, hypoxia, or hypoglycemia - and may culminate in loss of consciousness. Vertigo is typically described as spinning, rotating, or moving, but when the description is vague, the patient should be asked specifically if the symptom is associated with a sense of movement. The circumstances under which symptoms occur may also be diagnostically helpful. Vertigo is often brought on by changes in head position. The occurrence of symptoms upon arising after prolonged recumbency is a common feature of orthostatic hypotension, and nonvertiginous dizziness related to pancerebral hypoperfusion may be immediately relieved by sitting or lying down. Such hypoperfusion states can lead to loss of consciousness, which is rarely associated with true vertigo.

Differential Diagnosis

A. Anatomic Origin. The first step in the differential diagnosis of vertigo is to localize the pathological process in the peripheral or central vestibular pathways. Peripheral vestibular lesions affect the labyrinth of the inner ear or the vestibular division of the acoustic (VIII) nerve. Central lesions affect the brainstem vestibular nuclei or their connections. Rarely, vertigo is of cortical origin, occurring as a symptom associated with complex partial seizures.

B. Symptomatology. Certain characteristics of vertigo, including the presence of any associated abnormalities, can help differentiate between peripheral and central causes.

1. Peripheral vertigo tends to occur intermittently, last for briefer periods, and produce more distress than does vertigo of central origin. Nystagmus (rhythmic oscillation of the eyeballs) is always associated with peripheral vertigo; it is usually unidirectional and never vertical (see below). Peripheral lesions commonly produce additional symptoms of inner ear or acoustic nerve dysfunction, ie, hearing loss and tinnitus.

2. Central vertigo may occur with or without nystagmus; if nystagmus is present, it can be vertical, unidirectional, or multidirectional and may differ in character in the two eyes. (Vertical nystagmus is oscillation in a vertical plane; that produced by upgaze or downgaze is not necessarily in the vertical plane.) Central lesions may produce intrinsic brain stem or cerebellar signs, such as motor or sensory deficits, hyperreflexia, extensor plantar responses, dysarthria, or limb ataxia.

NEUROLOGIC EXAMINATION

A. Nystagmus and Voluntary Eye Movements. The patient is asked to turn the eyes in each of the cardinal directions of gaze (left, up and left, down and left, right, up and right, down and right) to determine whether gaze paresis (impaired ability to move the two eyes coordinately in any of the cardinal directions of gaze) or gazeevoked nystagmus is present. Nystagmus – an abnormal involuntary oscillation of the eyes – is characterized in terms of the positions of gaze in which it occurs, its amplitude, and the direction of its fast phase. Pendular nystagmus has the same velocity in both directions of eye movement; jerk nystagmus is characterized by both fast (vestibular-induced) and slow (cortical) phases. The direction of jerk nystagmus is defined by the direction of the fast component. Fast voluntary eye movements (saccades) are elicited by having the patient rapidly shift gaze from one target to another placed in a different part of the visual field. Slow voluntary eye movements (pursuits) are assessed by having the patient track a slowly moving target such as the examiner's finger.

1. Peripheral vestibular disorders produce unidirectional horizontal jerk nystagmus that is maximal on gaze away from the involved side. Central vestibular disorders can cause unidirectional or bidirectional horizontal nystagmus, vertical nystagmus, or gaze paresis. Cerebellar lesions are associated with a wide range of ocular abnormalities, including gaze pareses, defective saccades or pursuits, nystagmus in any or all directions, and ocular dysmetria (overshoot of visual targets during saccadic eye movements).

2. Pendular nystagmus is usually the result of visual impairment that begins in infancy.

B. Hearing. Preliminary examination of the acoustic (VIII) nerve should include otoscopic inspection of the auditory canals and tympanic membranes, assessment of auditory acuity in each ear, and Weber and Rinne tests performed with a 256-Hz tuning fork.

1. In the Weber test, unilateral sensorineural hearing loss (from lesions of the cochlea or cochlear nerve) causes the patient to perceive the sound produced by a vibrating tuning fork placed at the vertex of the skull as coming from the normal ear. With a conductive (external or middle ear) disorder, sound is localized to the abnormal ear.

2. The Rinne test may also distinguish between sensorineural and conductive defects in the affected ear. Air conduction (tested by holding the vibrating tuning fork next to the external auditory canal) normally produces a louder sound than does bone conduction (tested by placing the base of the tuning fork over the mastoid bone). This pattern also occurs with acoustic nerve lesions but is reversed in the case of conductive hearing loss.

C. Positional Tests. When patients indicate that vertigo occurs with a change in position, the Nylen-Barany or Dix-Hallpike maneuver is used to try to reproduce the precipitating circumstance. The head, turned to the right, is rapidly lowered 30 degrees below horizontal while the gaze is maintained to the right. This process is repeated with the head and eyes turned first to the left and then straight ahead. The eyes are observed for nystagmus, and the patient is asked to note the onset, severity, and cessation of vertigo.

Positional nystagmus and vertigo are usually associated with peripheral vestibular lesions and are most often a feature of benign positional vertigo. This is typically characterized by severe distress, a latency of several seconds between assumption of the position and the onset of vertigo and nystagmus, a tendency for the response to remit spontaneously (fatigue) as the position is maintained, and attenuation of the response (habituation) as the offending position is repeatedly assumed. Positional vertigo can also occur with central vestibular disease.

D. Caloric Testing. Disorders of the vestibuloocular pathways can be detected by caloric testing. The patient is placed supine with the head elevated 30 degrees to bring the superficially situated lateral semicircular canal into the upright position. Each ear canal is irrigated in turn with cold (33°C) or warm

(44°C) water for 40 seconds, with at least 5 minutes between tests. Warm water tends to produce less discomfort than cold. Caution: Caloric testing should be preceded by careful otoscopic examination; it is precluded if the tympanic membrane is perforated.

1. In the normal awake patient, cold-water caloric stimulation produces nystagmus with the slow phase toward and the fast phase away from the irrigated ear. Warm water irrigation produces the opposite response.

2. In patients with unilateral labyrinthine, vestibular nerve, or vestibular nuclear dysfunction, irrigation of the affected side fails to cause nystagmus or elicits nystagmus that is later in onset or brief er in duration than on the normal side.

E. Stance & Gait. Observation of stance and gait is helpful in distinguishing between cerebellar, vestibular, and sensory ataxias.

DISORDERS OF HEARING, DEAFNESS. TINNITUS

Deafness is usually caused by primary diseases of the middle ear, such as otosclerosis, otitis media, or trauma, or of the inner ear, such as noise exposure, various genetic causes, congenital rubella, and age-related presbyacusis. Unilateral deafness is often not noticed unless patients find they are unable to hear the telephone earpiece with that ear. The main neurological cause of deafness is a tumour affecting the eighth cranial (auditory) nerve in its course between the brainstem and the internal auditory meatus. Partial deafness is a common sequel to bacterial meningitis or other infiltrating processes in the meninges surrounding the nerve.

Tinnitus is a symptom in which the person hears noises in the ears or head in the absence of any sound stimulus. The subjective sensations can take many forms which include buzzing, humming, hissing, roaring, clicking, or some similar description. It is usually constant, but some patients describe it as intermittent, pulsating, or fluctuating.

Subjective tinnitus is an auditory sensation which is only heard by the patient, whereas objective tinnitus, which is much rarer, may be perceived by the examiner as well. The latter includes vascular causes, such as fistulae or arteriovenous malformations, or mechanical causes, as in palatal myoclonus.

Tinnitus is a symptom which, in addition to the common inner ear causes such as Meniere's disease, may herald a number of disorders, such as a glomus tumour, tumours of the internal auditory meatus or cerebellopontine angle, or a vascular abnormality in the temporal bone or skull.

VESTIBULAR DISORDERS

BENIGN POSITIONAL VERTIGO

Positional vertigo is vertigo that occurs upon assuming a particular head position. It is usually associated with peripheral vestibular lesions but may also be due to central (brain stem or cerebellar) disease.

Benign positional vertigo is the most common cause of vertigo of peripheral origin, accounting for about 30% of cases. The most frequently identified cause is head trauma, but in most instances, no cause can be determined. The pathophysiologic basis of benign positional vertigo is thought to be canalolithiasis-stimulation of the semicircular canal by debris floating in the endolymph.

The syndrome is characterized by brief (seconds to minutes) episodes of severe vertigo that may be accompanied by nausea and vomiting. Symptoms may occur with any change in head position but are usually most severe in the lateral decubitus position with the affected ear down. Episodic vertigo typically continues for several weeks and then resolves spontaneously; in some cases it is recurrent. Hearing loss is not a feature.

Peripheral and central causes of positional vertigo can usually be distinguished on physical examination by means of the Nylen-Baniny or Dix-Hallpike maneuver. Positional nystagmus always accompanies vertigo in the benign disorder and is typically unidirectional, rotatory, and delayed in onset by several seconds after assumption of the precipitating head position. If the position is maintained, nystagmus and vertigo resolve within seconds to minutes. If the maneuver is repeated successively, the response is attenuated. In contrast, positional vertigo of central origin tends to be less severe, and positional nystagmus may be absent. There is no latency, fatigue, or habituation in central positional vertigo.

The mainstay of treatment in most cases of benign positional vertigo of peripheral origin (canalolithiasis) is the use of repositioning maneuvers that employ the force of gravity to move endolymphatic debris out of the semicircular canal and into the vestibule, where it can be reabsorbed. In one such maneuver, the head is turned 45 degrees in the direction of the affected ear (determined clinically, as described above), and the patient reclines to a supine position, with the head (still turned 45 degrees) hanging down over the end of the examining table. The head, still hanging down, is then turned 90 degrees in the opposite direction, to 45 degrees toward the opposite ear. Next, the patient rolls to a lateral decubitus position with the affected ear up, and the head still turned 45 degrees toward the unaffected ear and hanging down. Finally, the patient turns to a prone position and sits up. Vestibulosuppressant drugs may also be useful in the acute period, and vestibular rehabilitation, which promotes compensation for vestibu-

lar dysfunction through the recruitment of other sensory modalities, may be helpful as well.

MENIERE'S DISEASE

Meniere's disease is characterized by repeated episodes of vertigo lasting from minutes to days, accompanied by tinnitus and progressive sensorineural hearing loss. Onset is between the ages of 20 and 50 years in about three-fourths of cases, and men are affected more often than women. The cause is thought to be an increase in the volume of labyrinthine endolymph (endolymphatic hydrops), but the pathogenetic mechanism is unknown.

At the time of the first acute attack, patients may already have noted the insidious onset of tinnitus, hearing loss, and a sensation of fullness in the ear. Acute attacks are characterized by vertigo, nausea, and vomiting and recur at intervals ranging from weeks to years. Hearing deteriorates in a stepwise fashion, with bilateral involvement reported in 10-70% of patients. As hearing loss increases, vertigo tends to become less severe.

Physical examination during an acute episode shows spontaneous horizontal or rotatory nystagmus (or both) that may change direction. Although spontaneous nystagmus is characteristically absent between attacks, caloric testing usually reveals impaired vestibular function. The hearing deficit is not always sufficiently advanced to be detectable at the bedside. Audiometry shows low-frequency pure-tone hearing loss, however, that fluctuates in severity as well as impaired speech discrimination and increased sensitivity to loud sounds.

As has been noted, episodes of vertigo tend to resolve as hearing loss progresses. Treatment is with diuretics, such as hydrochlorothiazide and triamterenen, vestibulosuppressants may also be helpful during acute attacks. In persistent, disabling, drug-resistant cases, surgical procedures such as endolymphatic shunting, labyrinthectomy, or vestibular nerve section are helpful.

ACUTE PERIPHERAL VESTIBULOPATHY

This term is used to describe a spontaneous attack of vertigo of inapparent cause that resolves spontaneously and is not accompanied by hearing loss or evidence of central nervous system dysfunction. It includes disorders diagnosed as acute labyrinthitis or vestibular neuronitis, which are based on unverifiable inferences about the site of disease and the pathogenetic mechanism. A recent antecedent febrile illness can sometimes be identified, however.

The disorder is characterized by vertigo, nausea, and vomiting of acute onset, typically lasting up to 2 weeks. Symptoms may recur, and some degree of vestibular dysfunction may be permanent.

During an attack, the patient – who appears ill typically lies on one side with the affected ear upward and is reluctant to move his or her head. Nys-

tagmus with the fast phase away from the affected ear is always present. The vestibular response to caloric testing is defective in one or both ears with about equal frequency. Auditory acuity is normal.

Acute peripheral vestibulopathy must be distinguished from central disorders that produce acute vertigo, such as stroke in the posterior cerebral circulation. Central disease is suggested by vertical nystagmus, altered consciousness, motor or sensory deficit, or dysarthria. Treatment is with a 10- to 14day course of prednisone, 20 mg orally twice daily, vestibulosuppressants.

OTOSCLEROSIS

Otosclerosis is caused by bony changes in the tympanic cavity that result in immobility of the stapes, the ear ossicle that normally transmits soundinduced vibration of the tympanic membrane to the inner ear. Its most distinctive clinical feature is conductive hearing loss, but sensorineural hearing loss and vertigo are also common; tinnitus occurs less frequently. Auditory symptoms usually begin before 30 years of age, and familial occurrence is common.

Vestibular dysfunction in otosclerosis is most often characterized by recurrent episodic vertigo-with or without positional vertigo-and a sense of positional imbalance. More continuous symptoms may also occur, and the frequency and severity of attacks may increase with time.

Vestibular abnormalities that can be seen on examination include spontaneous or positional nystagmus of the peripheral type and attenuated caloric responses. Abnormalities shown by caloric testing are usuall y unilateral.

Hearing loss is always demonstrable by audiometry. Usually of mixed conductive-sensorineural character, the loss is bilateral in about two-thirds of patients. In patients with episodic vertigo, progressive hearing loss, and tinnitus, otosclerosis must be distinguished from Meniere's disease. Otosclerosis (rather than Meniere's disease) is suggested by a positive family history, a tendency toward onset at an earlier age, the presence of conductive hearing loss, or bilateral symmetric auditory impairment. The CT scan may also be diagnostically useful.

Medical treatment with a combination of sodium fluoride, calcium gluconate, and vitamin D may be effective. If not, surgical stapedectomy should be considered.

HEAD TRAUMA

Head trauma is the most common identifiable cause of benign positional vertigo. Injury to the labyrinth is usually responsible for posttraumatic vertigo; however, fractures of the petrosal bone may lacerate the acoustic nerve, producing vertigo and hearing loss. Hemo-tympanum or CSF otorrhea suggests such a fracture.

CEREBELLOPONTINE ANGLE TUMOR

The cerebellopontine angle is a triangular region in the posterior fossa bordered by the cerebellum, the lateral pons, and the petrous ridge. By far the most common tumor in this area is the histologically benign acoustic neuroma (also termed neurilemoma, neurinoma, or schwannoma), which typically arises from the neurilemmal sheath of the vestibular portion of the acoustic nerve in the internal auditory canal. Less common tumors at this site include meningiomas and primary cholesteatomas (epidermoid cysts). Symptoms are produced by compression or displacement of the cranial nerves, brainstem, and cerebellum and by obstruction of CSF flow. Because of their anatomic relationship to the acoustic nerve, the trigeminal (V) and facial (VII) nerves are often affected.

Acoustic neuromas occur most often as isolated lesions in patients 30-60 years old, but they may also be a manifestation of neurofibromatosis. Neurofibromatosis I (von Recklinghausen's disease) is a common autosomal dominant disorder related to a gene defect on chromosome 17 (17q11.2). In addition to unilateral acoustic neuromas, neurofibromatosis I is associated with cafe-au-lait spots on the skin, cutaneous neurofibromas, axillary or inguinal freckles, optic gliomas, iris hamartomas, and dysplastic bony lesions. Neurofibromatosis 2 is a rare autosomal dominant disorder localized to chromosome 22 (22q11.1-13.1). Its hallmark is bilateral acoustic neuromas, which may be accompanied by other tumors of the central or peripheral nervous system, including neurofibromas, meningiomas, gliomas, and schwannomas.

Hearing loss of insidious onset is usually the initial symptom. Less often, patients present with headache, vertigo, gait ataxia, facial pain, tinnitus, a sensation of fullness in the ear, or facial weakness. Although vertigo ultimately develops in 20-30% of patients, a nonspecific feeling of unsteadiness is encountered more commonly. In contrast to Meniere's disease, there is a greater tendency for mild vestibular symptoms to persist between attacks. Symptoms may be stable or progress very slowly for months or years.

Unilateral hearing loss of the sensorineural type is the most common finding on physical examination. Other frequently noted abnormalities are ipsilateral facial palsy, depression or loss of the corneal reflex, and sensory loss over the face. Ataxia, spontaneous nystagmus, other lower cranial nerve palsies, and signs of increased intracranial pressure are less common. Unilateral vestibular dysfunction can usually be demonstrated with caloric testing.

Audiometry shows a sensorineural pattern of deficit with high-frequency pure-tone hearing loss, poor speech discrimination, and marked tone decay. CSF protein is elevated in about 70% of patients, usually in the range of 50-200 mg/dL. The most useful diagnostic radiologic study is MRI of the cerebellopontine angle. CT scanning is less sensitive. Acoustic neuromas sometimes cause abnormalities of the brainstem auditory evoked potentials at a time when radiologic studies show no abnormalities.

Treatment is complete surgical excision. In untreated cases, severe complications may result from brainstem compression or hydrocephalus.

TOXIC VESTIBULOPATHIES (ALCOHOL)

Several drugs can produce vertigo by their effects on the peripheral vestibular system. Alcohol causes an acute syndrome of positional vertigo because of its differential distribution between the cupula and endolymph of the inner ear. Alcohol initially diffuses into the cupula, reducing its density relative to the endolymph. This difference in density makes the peripheral vestibular apparatus unusually sensitive to gravity and thus to position. With time, alcohol also diffuses into the endolymph, and the densities of cupula and endolymph equalize, eliminating the gravitational sensitivity. As the blood alcohol level declines, alcohol leaves the cupula before it leaves the endolymph. This produces a second phase of gravitational sensitivity that persists until the alcohol diffuses out of the endolymph also.

Alcohol-induced positional vertigo typically occurs within 2 hours after ingesting ethanol in amounts sufficient to produce blood levels in excess of 40 mg/dL. It is characterized clinically by vertigo and nystagmus in the lateral recumbent position and is accentuated when the eyes are closed. The syndrome lasts up to about 12 hours and consists of two symptomatic phases separated by an asymptomatic interval of 1-2 hours. Other signs of alcohol intoxication, such as spontaneous nystagmus, dysarthria, and gait ataxia, are caused primarily by cerebellar dysfunction.

GLOSSOPHARYNGEAL NERVE (IX)

Although the glossopharyngeal nerve contains sensory, motor, and parasympathetic fibres, only its sensory function is testable at the bedside and for all practical purposes its other functions can be ignored. Functionally and anatomically it is closely related to the vagus nerve and, together with the accessory nerve, all three nerves may be affected by lesions in the jugular foramen. Isolated glossopharyngeal nerve lesions are rare, but this nerve alone is affected in the rare syndrome of glossopharyngeal neuralgia.

FUNCTIONAL ANATOMY

Three components of the glossopharyngeal nerve are of little interest in everyday clinical neurology. Special visceral afferent fibres subserve taste sensation from the posterior one-third of the tongue. Symptomatic loss of taste sensation from lesions of the nerve is not seen and there are no practical tests of this function at the bedside. General visceral efferent fibres give rise to parasympathetic fibres which stimulate secretion from the parotid gland. Special visceral efferent fibres innervate the stylopharyngeus, but this muscle cannot be assessed clinically.

Peripheral course

The glossopharyngeal nerve is formed by a series of radicles which enter and leave the medulla, in the posterior lateral sulcus, rostral to the vagus nerve. The nerve crosses the posterior fossa and leaves the skull, together with the vagus and accessory nerves, through the jugular foramen. It crosses in front of the internal carotid artery to reach the lateral wall of the pharynx. The nerve contains two peripheral ganglia, the superior ganglion which lies in the jugular foramen and the inferior (petrosal) ganglion which is extracranial. The ganglia contain the cell bodies of primary sensory neurons that subserve general somatic and general visceral sensation.

Sensory pathways

General visceral afferent fibres convey sensory impulses (tactile, thermal, and pain) from the posterior one-third of the tongue, tonsil, posterior wall of the upper pharynx and Eustachian tube, via the inferior ganglion, to the solitary fasciculus and its nucleus. Clinically, this particular sensory pathway is the most important function of the nerve and the only function readily assessed at the bedside. General somatic afferent fibres carry sensation from the posterior part of the ear, via the superior ganglion, and terminate in the spinal trigeminal tract and nucleus.

LESIONS OF THE GLOSSOPHARYNGEAL NERVE

As noted above, clinically the most important function of the glossopharyngeal nerve is its provision of sensory input from the upper pharynx. It thus provides the afferent limb of the gag or palatal reflex, the efferent limb of which is provided by the vagus. This reflex is too gross a test of glossopharyngeal function. If a lesion is suspected, the sensation on each side of the posterior pharyngeal wall should be tested using an orange stick or a firmly secured pin. Most patients will gag, and the palate will be seen to move, but what is more important is for the patient to state whether the sensation is the same on both sides.

Supranuclear and nuclear lesions

Supranuclear lesions have no specific discernible effect on glossopharyngeal nerve function, although involvement of stylopharyngeus may contribute to pseudobulbar palsy. Nuclear lesions in isolation are rarely, if ever, seen and other cranial nerve nuclei, particularly the vagus, are usually also involved. The most common cause is a vascular lesion, with other causes including primary and secondary neoplasia and syringobulbia.

Peripheral lesions

Between the medulla and jugular foramen the nerve may be affected by meningeal disease (e.g. inflammatory and neoplastic processes) and metastases. In the jugular foramen probably the most common lesion, which of course may also affect the vagus and accessory nerves, is a glomus tumour. Neuromas of any of these three nerves may arise in or near the jugular foramen and each nerve may be affected by basal skull fracture and basilar invagination. Metastatic disease may affect the nerve anywhere along its course, intracranially or extracranially.

GLOSSOPHARYNGEAL NEURALGIA

Although much rarer, glossopharyngeal neuralgia shares many similarities with trigeminal neuralgia with respect to aetiology, treatment, and the characteristics of the paroxysms of pain. Most cases are idiopathic but neuralgia may be symptomatic of lesions affecting the glossopharyngeal nerve, particularly neoplastic disorders, and there is evidence that new cases, like trigeminal neuralgia, may be caused by compression of the nerve by an aberrantly situated artery.

The paroxysms of pain may occur in clusters, with long periods of remission, or may be chronic. The pain is experienced in the back of the throat, below the angle of the jaw, and within the ear. The stabbing or lancinating quality is similar to that occurring in trigeminal neuralgia. Precipitants include eating, swallowing, talking, head turning, coughing, sneezing, and touching the outer ear. Syncope may occur in association with pain and is due to sinus bradycardia

or asystole, reflecting the intimate associations between the glossopharyngeal and vagus nerves.

The treatment of choice is carbamazepine, but if this does not work, or can not be tolerated, then the same drugs as used in trigeminal neuralgia (e.g. phenytoin, sodium valproate, baclofen, and lamotrigine) may be tried before resorting to surgical techniques, which include microvascular decompression, nerve section, and medullary tractotomy.

VAGUS NERVE (X)

FUNCTIONAL ANATOMY

The vagus nerve has the most extensive course of any of the cranial nerves and is anatomically complex, with different courses for the main nerve trunks and their branches on each side of the body. The nerve carries motor, sensory, and autonomic fibres, but with respect to structural lesions only the motor pathways are of great clinical importance. Disturbances of autonomic function are discussed elsewhere.

Sensory and autonomic pathways

General somatic afferent fibres subserve sensation from the skin over the back of the ear and the posterior wall of the external auditory meatus. The cell bodies are situated in the superior ganglion, which sits in or just below the jugular foramen, and centrally the fibres enter the spinal trigeminal tract in the medulla. General visceral afferent fibres, from the pharynx, larynx, trachea, oesophagus, and thoracic and abdominal viscera have their cell bodies in the inferior ganglion, and centrally the fibres enter the nucleus and tractus solitarius.

Preganglionic parasympathetic fibres (general visceral efferent) arise from the dorsal motor nucleus of the vagus nerve, situated in the floor of the fourth ventricle, and are destined to innervate the thoracic and abdominal viscera.

Motor pathways

Special visceral efferent fibres innervate the voluntary striated muscles of the pharynx and larynx. They originate in the nucleus ambiguus (which also gives rise to the special visceral efferent fibres of the glossopharyngeal nerve and cranial part of the spinal accessory nerve) which lies in the medullary reticular formation between the inferior olive and the spinal trigeminal nucleus.

Peripheral course

The trunk of the vagus nerve is formed by a series of rootlets which emerge from the medulla, anterior to the inferior cerebellar peduncle, in line

with the radicles of the glossopharyngeal and accessory nerves. The nerve leaves the skull through the jugular foramen, intimately associated with the accessory nerve and separated from the glossopharyngeal nerve only by a fibrous septum. In the neck it lies in the carotid sheath, initially between the internal carotid artery and internal jugular vein, and then between the common carotid artery and internal jugular vein. Below the root of the neck the course of the nerve is different on the two sides of the body.

On the right, the nerve crosses the subclavian artery and descends through the superior mediastinum posterior to the brachiocephalic vein and to the right of the trachea, to reach the posterior aspect of the lung root. On the left, the nerve passes between the common carotid and subclavian arteries to enter the thorax. It descends through the superior mediastinum, behind the phrenic nerve and brachiocephalic vein and crosses the left side of the aortic arch, reaching the posterior surface of the lung root.

The nerves branch behind the lung roots, and these branches unite with fibres from thoracic sympathetic ganglia to form the right and left posterior pulmonary plexuses. Fibres from these form the posterior and anterior oesophageal plexuses, respectively. Trunks, containing fibres from both vagus nerves, are reformed from these plexuses and pass into the abdomen, through the oesophageal opening, where they undergo complex further branching before supplying the abdominal viscera.

On each side, the vagus nerve has important branches arising in the jugular foramen, neck, and thorax. From the superior ganglion arises a meningeal branch, which innervates the dura in the posterior fossa, and an auricular branch which subserves sensation from the posterior auricle and external auditory meatus. The pharyngeal branch arises from the inferior ganglion and is the main motor nerve to the pharynx and soft palate. The superior laryngeal nerve also arises from the inferior ganglion. It has two branches: the internal, which is the main sensory nerve of the larynx, and the external, which is motor to the inferior pharyngeal constrictor and cricothyroid muscles. The recurrent laryngeal nerves have a different origin and course on each side of the body. On the right, this nerve arises from the vagus at the root of the neck, in front of the subclavian artery. It winds below and behind that vessel and ascends beside the trachea and behind the common carotid artery.

At the level of the thyroid gland the nerve is closely related to the inferior thyroid artery. On the left, the nerve arises from the vagus at the level of the aortic arch. It winds under the arch and then ascends along the side of the trachea. On both sides the recurrent laryngeal nerves ascend in a groove between the oesophagus and trachea, pass closely next to the medial surface of the thyroid gland, and enter the larynx to supply all of the laryngeal muscles except the cricothyroid.

LESIONS OF THE VAGUS NERVE AND ITS BRANCHES

Supranuclear, nuclear, nerve trunk, and branch lesions may affect swallowing and phonation, the exact pattern of symptoms depending upon the site and chronicity of the lesion.

Supranuclear lesions

Because the nuclei receive both crossed and uncrossed corticobulbar fibres, unilateral supranuclear lesions do not usually cause persisting problems with phonation and swallowing, although dysphagia may be prominent following an acute hemispheric stroke. Bilateral lesions are associated with the syndrome of pseudobulbar palsy, in which dysphagia and dysarthria are due to disordered movements of the pharyngeal and laryngeal (and tongue) muscles rather than frank paralysis. Common causes include upper brainstem or bilateral hemispheric strokes, motor neuron disease, and demyelination.

Nuclear lesions

A unilateral nuclear lesion will cause ipsilateral palatal, pharyngeal, and laryngeal paralysis. On phonation the soft palate does not rise on the affected side and the uvula is drawn to the normal side. Dysphagia is variable but usually mild. Phonation is affected not only because of laryngeal muscle weakness but also by accumulation of frothy mucus which collects near the opening of the oesophagus and overflows into the larynx as a result of impaired pharyngeal emptying. The voice and cough are weak and there is difficulty clearing the voice. Bilateral lesions, in the syndrome of bulbar palsy, produce much more severe symptoms. The speech is nasal and on attempting to swallow fluids regurgitate through the nose due to palatal weakness. There may be snoring and inspiratory stridor. Coughing is paralysed, leading to a high risk of bronchial aspiration. Acute bulbar palsy is life threatening and tracheostomy is required.

Unilateral nuclear lesions rarely occur in isolation and are usually accompanied by involvement of other cranial nerve nuclei and long tracts. Causes include vascular lesions (e.g. lateral medullary syndrome) and tumour. Bilateral nuclear lesions, sometimes asymmetric, may be due to vascular lesions, motor neuron disease, tumour, syringobulbia, encephalitis, poliomyelitis, and rabies.

Nerve-trunk lesions

The clinical features of a lesion affecting the vagus nerve trunk between its origin and the jugular foramen are as described above for a unilateral nuclear lesion. Thus, there is unilateral paralysis of the soft palate, pharynx, and larynx. Causes include primary (glomus jugulare, meningioma) and secondary tumour, meningitic processes, and basal skull fracture. There is frequently involvement of other cranial nerves (IX, XI, and XII).

The inferior ganglion lies just below the jugular foramen and from it arise the pharyngeal and superior laryngeal nerves, which supply the muscles of the soft palate and pharynx, and the tensors of the cords (cricothyroids). A lesion of the vagus nerve trunk below the inferior ganglion thus spares these muscles and

the pattern of laryngeal paralysis is the same as is seen with an isolated lesion of the recurrent laryngeal nerve.

Recurrent laryngeal nerve lesions

In practice, isolated vagus nerve trunk lesions are rare, but recurrent laryngeal nerve palsies are common. A unilateral lesion causes paralysis of the ipsilateral larynx and lower sphincter of the pharynx. The vocal cord is immobile and lies near the midline. Dysphagia is not a major feature, because the pharyngeal nerve is unaffected, although following an acute lesion there may be transient difficulties swallowing fluids. In the acute phase there may also be dysphonia but despite the paralysed vocal cord compensatory mechanisms are so efficient that the voice may remain or soon return to normal.

The left recurrent laryngeal nerve is more commonly involved than the right, as a result of mediastinal lesions, particularly neoplasia but less frequently aortic aneurysm and enlargement of the left atrium. In the neck the nerve may be affected unilaterally or bilaterally by trauma, surgery, cervical lymph gland enlargement (inflammatory or neoplastic), thyroid enlargement, and oesophageal carcinoma. Up to one-third of cases of recurrent laryngeal nerve palsy are idiopathic. They may be persistent or show partial or complete recovery.

ACCESSORY NERVE (XI)

This is a purely motor nerve. It is formed from cranial and spinal roots which, as the accessory nerve, run together for only a very short distance. The cranial component is essentially part of the vagus nerve and is distributed mainly to the pharyngeal and recurrent laryngeal branches of that nerve, whereas the spinal component innervates sternomastoid and trapezius.

FUNCTIONAL ANATOMY

The spinal nucleus of the accessory nerve lies in the lateral part of the anterior horn grey matter and extends from the pyramidal decussation to the fifth cervical segment. The fibres arising from it emerge from the lateral aspect of the cord, between the dorsal and ventral roots, and unite to form a trunk which ascends posterior to the denticulate ligament and enters the skull through the foramen magnum, dorsal to the vertebral artery. The cranial root is formed by nerve fibres arising from the lower part of the nucleus ambiguus. Rootlets emerge from the lateral medulla, below the origin of the vagus.

Peripheral course

The cranial and spinal components unite for a short distance and leave the skull through the jugular foramen, in close relationship to the vagus nerve to which the cranial root fibres are distributed. The spinal part runs backwards and laterally between the internal jugular vein and internal carotid artery and crosses the transverse process of the atlas. It passes deep to the sternomastoid muscle, which it supplies, and emerges from its posterior border from where it crosses the posterior triangle, lying on levator scapulae. In this part of its course it is quite superficial, thus subject to trauma, and also related to cervical lymph nodes. The nerve then passes under the anterior border of the trapezius and unites with branches of the third and fourth cervical nerves (C3 and C4) to form a plexus which innervates the muscle. The pattern of innervation of the different parts of trapezius is probably quite variable but, in general, the accessory nerve appears to supply the upper part of the muscle, and fibres derived from C3 and C4 supply the lower part.

LESIONS OF THE ACCESSORY NERVE

Unilateral sternomastoid weakness is asymptomatic because it normally acts in concert with other cervical muscles which can compensate. Bilateral, but otherwise isolated, nerve lesions must be vanishingly rare. Bilateral sternomastoid weakness, with symptomatic weakness of neck flexion, is seen in myotonic dystrophy, inflammatory myopathies, various muscular dystrophies, myasthenia gravis, and motor neuron disease, but in all of these cases other cervical muscles are also involved.

Trapezius weakness is symptomatic. The shoulder droops slightly and there is mild scapular winging at rest, with the scapular rotated outwards and downwards. The winging is exacerbated by abduction of the arm, whereas winging due to serratus anterior weakness is most evident on forward flexion of the arm. The patient notices difficulty in shrugging the shoulder, abducting the arm above 90° and carrying the extended arm backwards. Bilateral trapezius weakness causes the head to fall forwards. This is rarely the result of bilateral nerve-trunk involvement but is seen in myasthenia gravis, motor neuron disease, and various myopathies.

Supranuclear lesions

The cortical representation is mainly ipsilateral for sternomastoid and contralateral for trapezius. Thus, following a major hemisphere stroke, trapezius is weak on the paralysed side but sternomastoid is weak on the side of the hemispheric event.

Nuclear and nerve-trunk lesions

The spinal cord nucleus is rarely involved in isolation. The anterior horn cells may be affected by motor neuron disease and poliomyelitis and the nuclei may be compressed by upper cervical cord tumours and syringomyelia.

In the posterior fossa, lesions affecting the accessory nerve often also involve cranial nerves IX, X, and XII. Common pathologies include primary and secondary tumours, meningitic processes, and basal skull fracture through the jugular foramen.

Outside the skull the most common site of damage is in the posterior triangle (giving rise to trapezius but not sternomastoid weakness). The nerve may be damaged by trauma or during surgical procedures (particularly removal of cervical lymph glands) including carotid endarterectomy. Up to one-third of accessory nerve palsies are idiopathic, probably often as a forme fruste of neuralgic amyotrophy.

HYPOGLOSSAL NERVE (XII)

This motor nerve innervates all of the muscles of the tongue through general somatic efferent fibres. Although it contains some afferent fibres, their function is unclear and they are of no importance in clinical practice.

FUNCTIONAL ANATOMY

The nucleus, which is nearly 2 cm long, lies in the central grey matter of the medial eminence and extends from the stria medullaris to the most caudal part of the medulla. The axons arising from it pass ventro-laterally and emerge as a series of rootlets on the ventral aspect of the medulla between the inferior olivary complex and the pyramid.

Peripheral course

The rootlets pass behind the vertebral artery and unite as they exit the skull through the hypoglossal canal, which lies about 1 cm anterior, inferior, and medial to the jugular foramen. Immediately outside the skull the nerve is in close proximity to cranial nerves IX, X, and XI, the internal jugular vein, and the internal carotid artery. At the level of the angle of the mandible it sweeps antero-laterally, looping below the occipital artery and crossing the external carotid artery and then the loop of the lingual artery just above the hyoid bone. It then passes deep to the digastric muscle and terminates through multiple branches in the intrinsic and extrinsic tongue muscles.

LESIONS OF THE HYPOGLOSSAL NERVE

A unilateral lesion of the nucleus or nerve trunk causes ipsilateral wasting and weakness of the tongue. Fasciculation may be prominent, especially in infantile spinal muscular atrophy and classical motor neuron disease. The epithe-

lium is thrown into folds, which accumulate fur. In the acute stage, articulation and swallowing may be slightly impaired but chronic lesions are typically asymptomatic. The tongue deviates to the affected side on protrusion. Bilateral lower motor neuron lesions cause weakness of both sides of the tongue with inability to protrude the tongue, marked dysarthria, and mild swallowing difficulties. Such bilaterallesions are rare in isolation and are usually part of the syndrome of bulbar palsy, in which other bulbar muscles are affected and in which there is significant dysphagia. In one large series of cases of hypoglossal nerve palsy, 49 of 100 cases were due to tumour.

Supranuclear lesions

The nuclei have bilateral cortical representation so that a unilateral upper motor neuron lesion may have no observable effect, although occasionally the tongue may deviate to the contralateral side. Bilateral upper motor neuron involvement is seen as part of the syndrome of pseudobulbar palsy. The tongue is weak, clumsy, and contracted secondary to spasticity, but not wasted. Causes include bilateral hemispheric vascular disease, upper brain stem stroke and tumours, multiple sclerosis, and motor neuron disease.

Nuclear lesions

Unilateral nuclear damage may be caused by tumours or vascular lesions, in both of which cases other structures are usually involved. Thus, a vascular event in the lower medulla might cause a unilateral hypoglossal nerve palsy and contralateral hemiplegia due to corticospinal tract involvement. Bilateral, but sometimes asymmetric, hypoglossal nuclear lesions may result from vascular lesions, tumours, syringobulbia, spinal muscular atrophy, motor neuron disease, and poliomyelitis.

Nerve-trunk lesions

In the posterior fossa the hypoglossal nerve rootlets may be affected, often together with cranial nerves IX, X, and XI, by primary (e.g. glomus jugulare, meningioma) and secondary neoplasms and basal meningitic processes. Unilateral or bilateral palsies may arise as a result of congenital or acquired bony abnormalities around the foramen magnum (basilar impression, Paget's disease).

In the neck, the nerve may be damaged by external trauma, during surgery (including carotid endarterectomy), by tumours, and as a late consequence of radiotherapy to the region. Vascular causes include aberrantly placed arteries, carotid artery dissection, and as a complication of central venous catheterization. As with cranial nerves X and XI, idiopathic cases occur.

DYSPHAGIA

Difficulty in swallowing (dysphagia) is a common neurological problem and the most important sequelae include aspiration and malnutrition. Often it is these complications, particularly aspiration, that first draw the clinician's atten-

tion to the possibility of a swallowing disorder. Dysphagia may be due to mechanical factors, upper and lower motor neuron disorders, myasthenic syndromes, and myopathy.

Swallowing mechanisms

A complex sequence of movements, some voluntary but most involuntary or reflex, ensure that food is safely transferred from the outside world to the stomach. Normal swallowing depends upon the integrity of sensory and motor pathways of several cranial nerves: V, VII, IX, X, and XII. These events can be broken down into separate stages. In the first stage food is contained within the mouth, chewed, formed into a bolus, positioned on the tongue, and pushed into the oropharynx. The swallowing reflex is initiated as the bolus passes between the pillars of the fauces. The individual elements of this reflex include elevation of the soft palate (thus preventing nasal regurgitation), elevation of the larynx and closure of the entry to the trachea, and peristaltic propulsion of the bolus through the cricopharyngeal sphincter into the oesophagus. Coordinated peristalsis carries the bolus through the lower oesophageal sphincter, into the stomach.

Causes of dysphagia

In neurological practice dysphagia is most often seen in association with other, obvious, neurological problems. Apart from in oculopharyngeal muscular dystrophy, it is relatively rare as a sole presenting symptom, although occasionally this is seen in motor neuron disease, myasthenia gravis, and inclusion-body myositis. Conversely, in general medical practice, there are many mechanical or structural disorders which may have dysphagia as the presenting feature. In some of the disorders notably motor neuron disease, both upper and lower motor neuron dysfunction may contribute to the dysphagia.

Symptoms

The patient's description of their swallowing problem may give a clear indication as to the level of the problem. Oropharyngeal disorders cause symptoms on swallowing or immediately after-there may be nasal regurgitation, coughing, and choking due to aspiration, a sensation of blockage in the neck, and sometimes pain. With oesophageal problems, symptoms come on a little later and patients locate the site of blockage and discomfort to the lower throat or retrosternal region. As a generalization, obstructive causes of dysphagia, such as oesophageal carcinoma, initially give rise to greater problems with solids than fluids, whereas in neuromuscular disorders dysphagia for fluids may be a relatively early feature.

As noted above, when considering individual cranial nerves, unilateral upper or lower motor lesions generally do not cause major problems with dysphagia, particularly if of gradual onset. An important exception is the dysphagia, sometimes severe, seen transiently following hemispheric stroke. This is a major contributing factor to aspiration pneumonia.

It can not be overemphasized that aspiration may be silent, without symptoms such as coughing and choking, and without abnormal physical signs on bedside examination. If a patient with a disorder that might cause swallowing problems develops a chest infection then, even in the absence of specific features pointing towards such a problem, further investigation, such as videofluoroscopy, should be performed.

EXAMINATION AND INVESTIGATION

More often than not, the history and findings on examination (particularly those related to the lower cranial nerves) will identify the neurological disorder causing the dysphagia, or will at least point to the likely nature of the problem (e.g. a myopathy, neurogenic problem, or upper motor neuron disorder) and thus the direction of further investigations. In patients with mechanical oesophageal problems, physical examination may, of course, be normal. Endoscopy is of limited value in neurological practice, but of course invaluable when investigating structural disorders of the oesophagus.

CEREBRAL CORTEX AND NEUROPSYCHOLOGICAL DISORDERS

The diseases that disrupt the cerebral cortex and its subcortical connections result in a wide variety of clinical features, which include the classical syndromes of higher cortical dysfunction, such as the dysphasias, dyspraxias, amnesias, and agnosias, together with a wide variety of behavioural and emotional disturbances. Clinical investigation of such disorders frequently overlaps with the disciplines of clinical psychology and psychiatry. Historically there has been a broad split between those diseases that are seen by neurologists and those that are seen by psychiatrists. To some extent the distinction reflects the different clinical approaches employed; neurologists concentrate on the generality of disease caused by lesions in defined areas, whereas psychiatrists often deal with diseases that show a greater interaction with the individual's own personal history and place in society. In this chapter, disturbances of higher cortical function, the dementias, and behavioural aspects of neurological lesions are discussed. Awareness of the occasional presentation of psychiatric disease to the neurologist is important, and further details are available in textbooks of psychiatry. A review of clinical syndromes referable to identified areas of the cerebral cortex is followed by a functional approach, which discusses the main neuropsychological syndromes. The more generalized cognitive impairment seen with the dementias, such as Alzheimer's and Pick's diseases, are then reviewed, followed by areas of neuropsychiatric overlap.

Anatomy and physiology of the cerebral cortex

The human cerebral cortex consists of six laminae, comprising in total some 28×10^9 neurons and approximately the same number of glial cells: from the external surface, these are the molecular layer, the external granular, the external pyramidal, the internal granular, the internal pyramidal, and the multiform or fusiform layer. The interconnection of the neurons comprises a staggering 10^{12} synapses. Despite this dramatic development, the basic structural organization of the cerebral cortex in modular terms is the same across species. The basis of the modular organization is the minicolumn, representing some 80-100 neurons connected vertically, and within each minicolumn are all of the major cortical neuronal types. Two broad categories of neuronal cell types can be distinguished: the large pyramidal cells, which are the origin of the main outflow tracts and which utilize glutamate as the main neurotransmitter; and the smaller, non-pyramidal cells, which have predominantly local connections and primarily

utilize the inhibitory amino acid γ-aminobutyric acid, together with a variety of coexistent neuropeptides. There is an increasing sub categorization of the small non-pyramidal cells, and an increasing understanding of the intrinsic connectivity of these cells within the minicolumns. Cortical columns are minicolumns bound together by horizontal connections over a short range, which share physiological features based in part upon shared input and output characteristics. Layers 2 and 3 project to other cortical areas and layers 5 and 6 are primarily subcortical projections. Columns vary only from 300 to 600 μm in diameter across a very wide range of species. The expansion of the human brain is due to the increase of the total number of modular units rather than a difference in their size.

The organization of the cerebral cortex, in terms of the functional characteristics of the cortical columns, was established using single-cell recording for the somatic sensory cortex by Mountcastle, and the visual cortex by Hubel and Wiesel. The response characteristics of a somatic sensory column depend both upon modality and topography of the receptive fields. Similarly, in the visual cortex, columns can be defined by various properties of increasing complexity from ocularity and place through to orientation. This modular organization in anatomical and functional terms accords with the general view from cognitive psychology of modular processing. As the modular processing becomes more complex, the defining characteristics of the cortical column become the inputs from other columns, the outputs of which represent a further level of cortical processing. This achieves greatest complexity in the association cortices or homotypical cortical areas.

There is regional specialization within the cerebral cortex, which is reflected to some extent in architectonic differences, such as that originally identified by Brodmann (1909). However, particularly at the higher level of cortical processing, as represented by the association areas, cortical operations are also distributed. Evidence for distributed networks is provided both by functional brain imaging and by anatomical evidence of enormous convergent and reciprocal connections, for example those between the parietal and frontal cortex.

CLINICAL SYNDROMES ASSOCIATED WITH SPECIFIC AREAS OF THE CEREBRAL CORTEX

A number of clinical syndromes are recognized as characteristic of lesions in specific areas of the cerebral cortex. The syndromes largely, but not invariably, involve loss of function, although in some instances loss of inhibition may present as release phenomena. The descriptions of many of these clinical syndromes were derived from patients with discrete lesions due to ischaemic infarcts or tumours, and formerly required follow-up to post-mortem to determine

the location. Modern neuroimaging has considerably improved the power of such studies and there has been a spate of reports that locate specific syndromes to precise brain regions.

However, it should be emphasized that the observed associations are between clinical syndromes and brain areas and do not necessarily locate function to a specific brain region. Although a specific function may be lost following damage at a given site, the function itself is more likely to depend upon successful integration of a neural network. The particular area would be part of such a network and assumed to be of central importance.

In addition to the location of clinical syndromes to specific cortical areas, some syndromes may be better interpreted as representing disconnections of one area from another. The concept of disconnection syndromes was originally postulated by Dejerine and other early neurologists, and re-explored in considerable detail by Geschwind (1965). Some of the clinical syndromes arising from damage to the corpus callosum are most easily explained in terms of disconnection.

Functional imaging has contributed further to our knowledge of localization of function. Baseline measures of blood flow or cerebral glucose metabolism with positron emission tomography (PET scanning) can identify areas of reduced basal function when abnormalities on structural imaging may not be readily apparent. This has been most valuable in patients with frontal lobe degeneration. Activation studies can provide information on changes in cerebral blood flow, or deoxygenation of haemoglobin, and thus regions which are activated during a specific cognitive task relative to another. Such functional imaging studies have revealed that activation is often widely distributed, indicating that distributed networks are involved in such cognitive tasks. However, as with structure-function relationships, caution has to be exercised in their interpretation. Although lesion studies show areas which may be necessary for a particular function, they can only localize deficits and it cannot be inferred that the specific function occurs in that area. They will show areas and structures that are necessary, but not sufficient, for that function. Similarly, activation may occur in areas that are not necessarily essential to a function. For example, activation studies of language may show areas of increased blood flow in the right hemisphere and yet lesion studies indicate that dysphasia does not occur with lesions in the same area.

The most widely used activation studies involve subtraction paradigms. A baseline task is compared with an activation task that engages the cognitive component of interest. When the baseline data are subtracted, then areas that are activated are believed to relate directly to the particular cognitive component under study. More sophisticated models have been used to deal, for example, with language function, where it may be difficult to identify an appropriate baseline task. In these paradigms, referred to as cognitive conjunctions, areas of common activation rather than areas of different activation are sought. Functional imaging has provided valuable insights into the distributive networks in-

volved in many cognitive processes, such as language. It does, however, remain a research tool and as yet has had limited impact on routine neurological management.

The frontal lobes

The frontal lobes lie rostral to the central sulcus and superior to the Sylvian fissure. They show the greatest development in humans, compared with other primates. Within the frontal lobes are the primary motor cortices, located within the precentral area, together with the supplementary motor areas and the frontal eye fields. The dominant frontal lobe encompasses Broca's area and the adjacent area of the motor cortex is involved with the motor control of the oropharynx, lesions of which result in impairment of articulation and phonation. However, the prefrontal cortex, Brodmann areas 9, 10, 11, 12 and 45, 46 and 47, is particularly developed in humans and yet has a less clearly defined function.

The frontal cortex has widespread connections with other areas of the brain. The pyramidal cells of the motor cortex form the major fronto-striatal outflow tract and, similarly, there are extensive projections from subcortical structures into the frontal cortex, notably the dopaminergic, noradrenergic, and cholinergic cortical projection systems.

Early studies with experimental frontal lobe lesions in nonhuman primates revealed impaired performance on a number of tasks which suggested perseverative responses and difficulty in switching between preferred modes of response. These difficulties with switching cognitive sets were explored further using the Wisconsin card-sorting test. Patients tend to perseverate on these tasks and yet on other tasks, such as cognitive estimates, patients may be quite impulsive and unable to monitor their performance.

The combination of perseverative responses, lack of initiative, and impulsivity has been brought together in the hypothesis of a supervisory attentional system for the frontal lobes. In this model, the frontal lobes have an important role in both selecting appropriate behavioural responses and inhibiting inappropriate ones. This can explain the paradoxical combination of both aspontaneity and lethargy together with impulsivity, even within the same patient. Breakdown in such a system results in markedly impaired social behaviour and adaptability, and yet formal testing shows that intelligence may often be spared. One of the most distinctive features of the frontal lobe syndrome is a change in personality, most commonly towards disinhibition. The effect upon personality of massive bifrontal lesions was well demonstrated by the celebrated case of Phineas Gage who, in 1848, had a crowbar driven through the front of his skull. He was described as 'fitful, irreverent, indulging at times in the greatest profanity ... manifesting but little deference for his fellows, impatient of restraint or advice when it conflicts with his desires, at times pertinaciously obstinate, yet capricious and

vacillatory'. Thus a frontal lobe syndrome has come to be recognized: an affected individual previously capable of judgement and sustained application and organization of his life, may become aimless and improvident, with loss of tact, sensitivity, and self-control, and with impulsiveness and a failure to appreciate the consequences of reckless behaviour. The disinhibited behaviour may result in childish excitement (moria) or joking and pathological punning (Witzelsucht); there may in addition be sexual indiscretions and exhibitionism. Alternatively, the syndrome may present with lack of initiative and profound psychomotor slowing (abulia). This may be accompanied, particularly with bifrontallesions, by urinary incontinence, which can occasionally be seen with unilateral lesions. This incontinence is commonly associated with lack of concern and social awareness, which is a useful clinical clue since this type of incontinence is rarely found with generalized dementing conditions such as Alzheimer's disease.

The behavioural disturbance can be striking, and can precede changes on formal tests of frontal lobe function by many years. A distinction has been drawn between dorsolateral frontal lesions, which may be associated with cognitive decline and apathy, and/or orbitomediallesions with prominent behavioural change. Often the changes in behaviour are most apparent to the spouse, who may feel that they are married to somebody entirely different.

Clinical examination may be less revealing than the history, and often patients perform relatively well on formal tests of intelligence. However, specific tasks, such as the Wisconsin card sorting test, the Weigl sorting test, cognitive estimates, verbal fluency, and bimanual motor tasks, will show impairment, but even this may be patchy and inconsistent. The patient's appearance may be clearly abnormal, appearing unkempt, unwashed, and lacking all spontaneity. Neurological examination may reveal primitive reflexes, such as the rooting reflexes, both tactile and oral, and sucking reflexes, if severe. Grasp reflexes are easily elicited by running the hand across the palm and may be elicited from the foot. The grasp reflex and instinctive grasp reaction can be seen as part of a more generalized magnetic behaviour, elicited as utilization. This is a striking example of environmental dependency, in which presentation of an object will elicit a behavioural response regardless of whether or not it is appropriate. Patients offered spectacles, for example, may place them on their nose, followed by further pairs, until three or four are stacked upon one another, the inappropriateness of this completely eluding the patient.

As lesions extend more posteriorly in the dominant frontal lobe, there may be an associated non-fluent anterior dysphasia and impairment of speech production. Lesions in relation to the orbital surface may result in unilateral visual failure and anosmia. The latter will rarely be found unless specifically sought and is a characteristic feature of olfactory groove meningiomas. On examination, prominent changes in tone may be found which increase in response to the stimulus, so-called paratonia or Gegenhalten. More posteriorly placed lesions may result in mild pyramidal signs, but most striking are bifrontal medial lesions

causing prominent gait impairment with truncal instability, often referred to as gait apraxia. With the availability of CT and MRI scanning, frontal lobe tumours are far more readily diagnosed.

However, with the gradual onset of personality changes, many cases are still missed until late. In general, frontal lobe syndromes are seen more commonly with tumours and degenerative disease than with vascular disease.

The temporal lobes

The Sylvian fissure separates the temporal lobe from the frontal lobe and rostral part of the parietal lobe. There is, however, no clear boundary between the posterior temporal lobe and the parietal and occipital lobes. The temporal lobes have easily discernible gyri – the superior, middle, and inferior temporal gyri – and also the parahippocampal and hippocampal convolutions. The hippocampus demonstrates a three-layered cortical structure, in contrast to the six-layered neocortex. Heschl's gyrus in the Sylvian fissure represents the primary auditory receptive area, and fibres terminating here do so in a tonotopic arrangement. Deep within the temporal lobe is the amygdala.

Discrete lesions of the anterior temporal poles may be clinically silent and, in general, lesions of the non-dominant temporallobe are less obvious clinically; sometimes the only clue on neurological examination being a superior quadran tic visual field defect or behavioural change. However, bitemporal lesions and those of the dominant temporal lobe may result in profound functional impairments. The predominant lesion of the dominant temporal lobe is that of a language impairment, classically a Wernicke's aphasia or, rarely, a pure word deafness or auditory verbal agnosia.

Unilateral lesions of the dominant temporal lobe can be shown to result in impairment of memory for verbal material, by contrast to impaired visual memory with non-dominant lesions. Unilateral lesions of Heschl's gyrus rarely result in deafness, but careful binaural testing reveals subtle abnormalities in the area contralateral to the lesions. The inability to recognize faces, prosopagnosia, is usually seen with bilateral lesions but has also been described with unilateral non-dominant temporoparietal lesions. Patients with prosopagnosia may have a variety of deficits, ranging from an inability to recognize the face through to loss of familiarity and inability to match faces. This can sometimes be so severe that patients are incapable of recognizing members of their own family but can do so immediately on hearing their voices.

Very rarely, lesions of the temporal lobe can result in a true auditory agnosia. Simple perception of sound and pure tone is intact but the interpretation of complex sounds is severely impaired. In pure auditory agnosia recognition of all noises, for example the sound of a bell, dogs barking, or running water, is lost. More common is the loss of appreciation of music, or amusia, seen with

right temporal lobe lesions. The patient's appreciation of melody, timbre, and rhythm all tend to be impaired and they may also have difficulty in musical recognition.

Bilateral temporal lobe lesions are far more devastating. These cases are rare and occur after herpes encephalitis or in the later stages of frontotemporal degeneration. They are normally associated with a dysphasia and, in addition, profound memory impairments. Bilateral removal of the temporal lobes in the monkey produces a striking behavioural state referred to as the Kluver-Bucy syndrome. The monkeys show increased exploratory behaviour, in which they will examine objects by oral and manual manipulation with apparent inability to recognize them visually. They are usually placid but with hypersexuality. Similar cases have been described with herpes encephalitis and with frontotemporal degenerations. The frontotemporal degenerations encompass a variety of disease processes, including Pick's disease. They are often associated with obsessional behaviour, change in eating habits, hypereligiosity, and both hypo- and hypersexuality. Some of these features may reflect involvement of the amygdala.

A variety of episodic symptoms may be found with temporal lobe lesions, which are usually on an epileptic basis and range from auditory hallucinations to disruption of time perception and disturbances of sexual behaviour. In addition, however, chronic bilateral lesions, particularly those of the medial temporallobes, may cause profound disintegration of personality and behaviour. In its extreme form patients react to any stimulus by excessive rage with screaming, biting, and spitting. This distressing clinical picture is seen most commonly in survivors of herpes encephalitis.

The parietal lobes

The parietal lobes lie behind the central sulcus and above the Sylvian fissure, but the posterior boundaries with the occipital and temporal lobes are not clearly defined. Immediately behind the central sulcus is the primary sensory cortex, which is delineated posteriorly by the post central sulcus. The superior temporal sulcus curves upwards posteriorly into the inferior parietal lobule in relation to the angular gyrus. This is adjacent to the posterior extremity of the Sylvian fissure, which also curves up into the inferior parietal lobule in relation to the supramarginal gyrus. The supramarginal and angular gyri, together with the posterior third of the superior temporal gyrus, constitute the Wernicke speech area. The parietal lobes are well developed in humans and continue to develop until about the seventh year of life. There are extensive connections with other association areas.

Lesions within the parietal lobes can present with an enormous variety of disturbances of higher cortical function, some of which are quite dramatic in their presentation. Dominant parietal lobe lesions are often associated with dys-

phasia. This may be predominantly a motor or sensory dysphasia, depending upon the antero-posterior location. More posterior lesions are associated with dyslexia, dysgraphia, and dyscalculia, and ideational apraxia is a consistent feature of dominant parietal lobe lesions. Gerstmann's syndrome refers to the association of finger agnosia, dyscalculia, right-left disorientation, and agraphia. Although this is commonly seen with lesions of the dominant angular gyrus, this particular clustering of deficits is no more common than other patterns. Lesions of either parietal lobe may result in visuospatial disturbance and topographical disorientation. Similarly, both parietal lobes are involved with selective attention. However, it is with lesions of the non-dominant parietal lobe that the most striking disturbances of visuospatial function and disturbances of body image are seen. Patients with non-dominant parietal lesions have marked impairment of selective attention which will affect both right- and left-sided space, but most commonly left-sided space. This may be so severe that they will ignore the left side of the body, resulting in problems in dressing, and in shaving only one half of their face. If this is associated with a left hemiplegia, they may be unaware of the deficit (anosognosia) and indeed deny that the paralysed limb has anything to do with them.

On examination, patients with parietal lobe lesions may show the obvious neglect of the left side, with an arm hung loosely at the side or out of the sleeve of their jacket, with the left face unshaven, and associated pyramidal signs. Field defects are most commonly inferior quadrantanopias. Gaze impersistence, an inability to sustain lateral gaze on testing eye movements, is seen quite commonly and can be very frustrating for the examiner. Cortical sensory loss may be found in the contralateral limbs, which can be most readily picked up by testing two-point discrimination, which is impaired together with astereognosis (inability to recognize objects by their shape), or alternatively inability to recognize figures written on the hand (agraphesthesia). Neglect can be unmasked by simultaneous tactile or visual stimuli, when the patient may only recognize one of the two simultaneously presented stimuli, ignoring that contralateral to the lesion. The sensory testing may be difficult, with patients showing considerable variability and being easily fatigued. Simple bedside tests of visuospatial function that can be helpful include drawing a cube or clock face, when patients will often ignore features to the left-hand side. Dressing apraxia can be assessed by watching the patient put on clothing, and the task made more difficult by inverting one sleeve.

The occipital lobes

The occipital lobes are separated on the medial surface from the parietal lobes by the parieto-occipital fissure, but there are no clearly defined margins between the parietal and temporal lobes on the lateral surface. The occipital lobes subsume the termination of the visual pathways, and the primary visual

cortex, Brodmann area 17, lies on either side of the calcarine fissure, which runs from the occipital pole to the splenium of the corpus callosum. It has the histological characteristic that its fourth layer is divided into two granular cell layers by a thickened band of heavily myelinated fibres, the external band of Baillarger. This band is visible to the naked eye, hence the name of striate cortex. The classical findings with lesions of the occipital cortex are homonymous visual field defects; a homonymous hemianopia when confined to one occipital lobe. Bilateral lesions may cause altitudinal defects, since the termination of the optic radiation is topographically arranged, with lower retinal fibres terminating in the cortex below the calcarine fissure. Superior quadran tic defects are found with inferior lesions and vice versa.

With extensive bilateral lesions various abnormalities are found, ranging from complete cortical blindness, through to subtle visual disturbances. With complete cortical blindness, the pupillary responses are preserved, as is visual imagery in dreams, but cortical evoked responses and the alpha rhythm on the EEG are both lost. Strikingly, patients with complete cortical blindness may develop a visual anosognosia (Anton's syndrome) with denial of their loss of sight. These patients may walk around as if they can see but will bump into objects and often explain their difficulties by complaining about the light or their loss of glasses. With partial recovery from cortical blindness, or with lesions involving the visual association areas, there may be a variety of disturbances of higher visual processing. These may fractionate into distinct syndromes such as visual disorientation, in which the ability to locate objects within the visual field is considerably impaired and patients may be effectively blind. This forms a major component of Balint's syndrome, in which patients have an inability to direct gaze into the peripheral field despite full eye movements, a visual inattention affecting the periphery of the visual field, and prominent optic ataxia, in which there is failure to grasp or touch an object under visual guidance. Other syndromes involve selective loss of colour, achromatopsia, and (very rarely) impairment of movement perception. Rarely patients may develop genuine visual object agnosia if the lesion involves the occipitotemporal areas. These patients are unable to recognize objects by sight, but can do so on palpation or by sound. The lesions are usually bilateral but may be found with dominant lesions.

Patients may complain of a variety of visual hallucinations and illusions, more commonly with bilateral or non-dominant lesions. Many of these are associated with epileptic phenomena, such as elementary unformed hallucinations and flashes of light, colours, or geometric forms. They may be seen within the setting of a hemianopic disturbance. Striking visual illusions may occur with metamorphopsias and marked changes in shape. In addition polyopia (multiple images) may be seen, or the striking disturbance of palinopsia, in which perserveration of visual images occurs and colour may spread outside the geometric confines of the object.

Subcortical syndromes

Although the cerebral cortex is viewed as the main seat of cognitive behaviour, it is becoming increasingly recognized that damage to subcortical structures can give rise to profound behavioural and cognitive disturbance. In many instances, these may mimic deficits arising from lesions within the cerebral cortex, for example the dysphasia and dyspraxia which may be seen with dominant thalamic lesions. These may share characteristics with cortical lesions by virtue of the extensive neural interconnections; an interpretation supported by observed changes in metabolism within connected areas of the cerebral cortex demonstrated on SPECT scanning subsequent to subcortical infarcts. Many of the behavioural disturbances are discussed elsewhere under the appropriate sections, but some structures are particularly notable. The importance of the amygdalae in behaviour has already been referred to, and rare instances of a Kluver-Bucy syndrome have been described. In addition, bilateral damage to the amygdalae can result in disturbance of memory as well as disturbed social behaviour and impaired recognition of emotional facial recognition; the latter may contribute to some of the social behavioural disturbances seen in frontotemporal degeneration.

Disease of the basal ganglia can give rise to prominent cognitive and conative dysfunction, most commonly observed with massive destructions following haemorrhage, infarcts, or intoxications. Bilateral thalamic infarcts are dominated by disturbances of attention, but fluctuating aphasia is characteristic of left-sided lesions, whereas right thalamic infarcts can result in the 'left neglect' syndromes which mimic non-dominant parietallesions. Thalamic haemorrhages tend to be more dramatic in their presentation and usually cause a relatively fluent aphasia with marked fluctuation and superimposed hypophonia. Caudate lesions are more commonly associated with behavioural disturbances, usually abulia, than with motor syndromes. A syndrome of dysphasia with dysarthria and orofacial dyspraxia can occur with dominant head of caudate infarcts, and dysphasic syndromes can also occur with lesions of the adjacent white matter or internal capsule. Apraxia is very rare with lesions confined to basal ganglia, but can be seen more commonly with lesions of the thalamus. Bilateral lesions of the basal ganglia can result in profound behavioural disturbance. Marked apathy, similar to a frontal lobe syndrome, can occur with bilateral lesions of the globus pallidus, so-called pure psychic akinesia. Bilateral infarction of the head of caudate has resulted in severely aggressive and criminal behaviour. Occlusions of the basilar artery at the bifurcation, the socalled 'top of the basilar' syndrome, result in complex disorders of eye movement, with convergent spasm, retraction nystagmus, and skew deviation. It is commonly accompanied by memory disturbance and an agitated confusional state with prominent visual hallucinations, so-called peduncular hallucinosis.

NEUROPSYCHOLOGICAL SYNDROMES

In the preceding section clusters of neuropsychological deficits which are characteristic of damage to particular areas of cerebral cortex were described. Often relatively pure deficits may present to neurologists, and more detailed understanding of the precise nature of the functional impairment, over and above the localizing significance, can be helpful in diagnosis and management.

Disorders of perception and the agnosias

In 1890, Lissauer introduced the terms apperceptive and associative 'mind blindness' to distinguish between patients whose abilities to perceive and discriminate an object are impaired, and those patients who are unable to recognize the object having correctly perceived it. The following year, Freud introduced the term agnosia, which subsequently replaced the term 'mind blindness'.

Visual agnosias have been most widely studied and Lissauer's original analysis has subsequently proved useful in the analysis of neurological patients. In order to perceive an object, a number of features must be analysed and processed, such as shape, colour, location within space, and movement; these may each be selectively damaged. Shape discrimination can be assessed by asking the patient to discriminate between rectangles and squares of increasing similarity. Preservation of shape and location but with loss of colour (achromatopsia) is rare, and is usually seen with bilateral damage to the fusiform and lingual gyri. There is commonly an associated superior altitudinal field defect. Impairment of visual location, visual disorientation, can cause great impairment and render the patient functionally blind. Finally, patients have very rarely been described with inability to detect movement, indicating a further dimension of early visual processing.

These abnormalities of early visual processing are most commonly seen with bilateral occipital and occipitoparietal lesions, but can be seen with unilateral lesions, in which case the deficit is found in the contralateral field of vision. In these instances the functional impairment may be less prominent and patients less likely to present with a specific history. These disorders of visual processing are usually due to ischaemic lesions, but visual disorientation can be found in degenerative lesions of the occipital and parietal cortex, sometimes referred to as posterior cortical atrophy, which can be a presenting feature of Alzheimer's disease.

In apperceptive agnosia there is impairment of the generation of a structured percept of an object despite adequate initial processing of shape, colour, and location. This impairment can be demonstrated in patients who have diffi-

culty coping with perceptually difficult visual stimuli, such as incomplete line drawings, overlapping line drawings, fragmented letters, and unusual views. Unlike the retinotopic organization of early visual processing, the entire visual field is involved in patients with apperceptive agnosia, and the minimal lesion is usually found in the posterior non-dominant parietal lobe.

Associative visual agnosia is very rare. Patients can describe an object very well and copy drawings of it precisely but it has no meaning for them. They are, however, able to recognize the object immediately through other sensory channels. Patients with visual agnosia usually have bilateral lesions, but these can occur with unilateral left posterior parietal lesions. Classically, visual agnosia has been interpreted as a disconnection of the percept from a central meaning system, but an alternative interpretation is the existence of modality-specific meaning systems, and visual agnosia would thus be seen as a loss of the specific meaning system associated with the visual domain, i.e. a visual semantic memory impairment.

Within the overall category of visual agnosias, some defects have been singled out for particular consideration because they present as striking clinical deficits; examples include the inability to recognize colour (colour agnosia) and inability to recognize faces (prosopagnosia). Colour agnosia implies intact colour perception and semantic knowledge of colour, but the majority of cases appear to have an associated impairment of colour naming. Faces present a perceptually difficult visual task and, clearly, problems in visual processing and perception will result in difficulty in face recognition. However, some patients present with a relatively selective impairment of facial recognition. Such cases can present a striking clinical picture, in that patients may be unable to recognize those very close to them, but can immediately do so when they hear them speak, or by looking for other clues in their dress or mannerisms. Prosopagnosia is usually associated with right occipitotemporal lesions and is commonly associated with a left homonymous superior quadrantanopia. Pro sop agnosia can be analysed in a similar way to object recognition-employing tests to assess perceptual analysis, such as matching pictures of faces and matching facial expressions. Some patients may have normal performance on face-matching tasks but be quite unable to recognize familiar faces. Others may show intact face matching but be unable to match facial expression. These theoretical aspects of pro sop agnosia have generated a number of information-processing models of face recognition.

Agnosias in other sensory domains have been far less well studied and have a less secure theoretical basis. Cortical deafness can occur with bilateral temporal lesions which result in deficits of discrimination, temporal sequencing, and spatial localization of sound. Pure word deafness as an isolated agnosia for speech sounds usually overlaps with Wernicke's aphasia. Auditory agnosia is extremely rare and refers to patients with intact hearing and intact language comprehension but who are unable to recognize meaningful nonverbal sounds. Fol-

lowing Lissauer's original terminology, these have also been divided into apperceptive and associative agnosias.

Tactile agnosia is even less secure as a distinct syndrome. Patients with parietal lesions will often have difficulty with the appreciation of size, texture, and shape of objects held in the hand, and astereognosis, which is more strictly referred to as stereoanasthesia or stereohypoasthesia. These patients will have impairment of two-point discrimination and sometimes subtle proprioceptive changes. Strictly speaking, astereognosis should exist when shape and discrimination is intact, as evidenced by the patient's description, but recognition impaired. Astereognosis, however, may occur as a disconnection syndrome in patients with callosal lesions. In such patients objects can be recognized in the right hand but not in the left; they can, however, be correctly identified from a visual array. This is interpreted as disconnection of the sensory information from the right parietal cortex reaching the left hemisphere language area.

Disorders of spatial awareness and the body image

We are aware of the existence of our bodies, their position in space, and the relation of their parts to one another because we receive data through numerous sensory channels; these include vision, cutaneous sensibility, and proprioceptive information from the muscles, joints, and labyrinths. The somatic impulses pass via the ventral nucleus of the thalamus to the supramarginal gyrus, which is thus concerned with awareness of the opposite side of the body. This concept of the body in consciousness is known as the body image or body schema.

Symptoms of disorders of the body image may be positive or negative. The chief positive symptom is the phantom-an illusion of the persistence of a part of the body lost by amputation, e.g. a phantom limb, or an illusory awareness of a part from which sensation has been lost through interruption of afferent pathways. Phantom limbs after amputation may be painless or painful. The painless phantom soon becomes less obtrusive, and gradually shortens, eventually to disappear. Painful phantoms may persist indefinitely and cause much distress.

Impairment of spatial sense together with neglect is most commonly seen following right parietal lesions and can present a dramatic clinical picture. Such patients frequently manifest spatial disorientation both for external space and for the body image, and, within hospital, mislocate their bed. These patients often have an associated left hemiparesis, again indicating a relationship with the nondominant parietal lobe. Patients with right hemisphere lesions exhibit neglect that is most obvious to the left side of the body and left space, and these patients may not shave the left side of their face, may eat food only on the right side of the dinner plate, and may demonstrate neglect dyslexia. Most striking is inatten-

tion to left-sided deficits, such as left hemiparesis, so called anosognosia. In a less severe degree of negelect, patients may recognize their left hemiparesis but are unconcerned, a complication which can make rehabilitation extremely difficult.

There are two main theories of spatial neglect in association with lesions of the non-dominant parietal lobe. One proposes that there is a central representation of space, which is damaged; the other proposes that there is a defect of selective attention, a function for which the right hemisphere is dominant.

Apraxia

Apraxia may be defined as the inability to carry out a purposive movement, the nature of which the patient understands, in the absence of severe motor weakness or paralysis, sensory loss, or ataxia. For example, a patient who is asked to protrude his tongue is unable to do so on request, although he may carry out inappropriate movements such as opening his mouth. A moment later he spontaneously protrudes his tongue to lick his lips. Apraxia may involve any movement that is normally initiated voluntarily – movements of the eyes, face, muscles of articulation, chewing and swallowing, manipulation of objects, gestures with the upper limb, walking, or sitting down. Apraxia is seen most commonly with left hemisphere lesions, and is then found in association with dysphasia.

The terminology of apraxia is particularly confusing since it includes a number of conditions that are not genuinely apraxic and, additionally, employs terms that are derived from the theoretical framework developed by Liepmann at the turn of the century. He defined three types of apraxia, namely limbkinetic, ideomotor, and ideational. These were based upon a theoretical neuroanatomical model similar to those that have been developed for speech. Limb-kinetic apraxia is rarely used and probably reflects a mild pyramidal lesion. Ideomotor dyspraxia refers to the poor performance of a motor act in response to a verbal command. This is most commonly explored at the bedside by asking patients to mime. It has been interpreted in terms of disconnection, although the most secure disconnection model for ideomotor dyspraxia is seen in patients with lesions of the anterior corpus callosum, who have difficulty with performing tasks to command using the left hand, i.e. the 'praxis centre' in the left hemisphere is disconnected from the right motor cortex which controls the left hand. This is sometimes referred to as callosal apraxia and is commonly seen with anterior cerebral artery infarcts.

Ideational apraxia was defined by Liepmann as an inability to perform a sequential motor act, even though each could be carried out separately. However, this is relatively non-specific and may be a feature of frontal lobe lesions, reflecting a difficulty of programming rather than of dyspraxia. De Renzi *et al.*

(1968) have defined ideational apraxia as an impairment in manipulation of actual objects. Subsequently, De Renzi has postulated that these patients have an agnosia for tool usage which, in this context, is associated with lesions of the posterior dominant parietal lobe. Patients with clinically obvious apraxia are relatively rare but severely disabled. They have considerable difficulty using a knife and fork and with many other common tasks which require manual dexterity, and they will often look at their hands in a bemused way. By contrast, patients who demonstrate ideomotor dyspraxia at the bedside may not be functionally disabled, representing merely a feature of a specific neurological examination.

In addition to the syndromes described above, which relate to manual dexterity, other body-part dyspraxias have been described. A dissociation between limb apraxia and an axial dyspraxia, demonstrated by difficulty with adopting truncal postures such as a boxer's stance, has been described. Patients with gait apraxia show severe impairment of walking and often of standing, with additional truncal instability. Orofacial dyspraxia is found with dominant frontal lesions and often associated with a cortical dysarthria; such patients show a characteristic inability to make oral movements to command but with sparing of eye movements. When asked to cough they will frequently repeat the word 'cough'; however, they will be observed to carry out such motor acts spontaneously. This may be seen on a degenerative basis. Dressing apraxia is associated with non-dominant parietal lobe lesions and is normally seen in a context of spatial impairment and left-sided neglect.

Constructional apraxia refers to a disorder of the spatial disposition of an action and is illustrated at the bedside by inability to copy a cube or to make a simple arrangement of matches. This was originally identified as a disconnection syndrome between spatial analysis and voluntary action. This remains to be proven, and apparent constructional apraxia may be due to more than one defect. Patients with left hemisphere lesions may make dyspraxic errors and commonly they will retain the spatial organization but simplify a diagram, whereas those with right hemisphere lesions show impairment of the spatial organization and will often neglect the left side.

Dysphasias

Since so much of the complexity of human behaviour depends upon language, impairment in this domain often presents early and with striking features. Historically the language disorders were also the first to be associated with precise focal brain lesions. The terms 'dysphasia' and 'aphasia' are often used interchangeably. American usage favours 'dysphasia' for developmental or congenital language disorders, reserving 'aphasia' for the acquired disorders of language. In Europe 'dysphasia' has been applied in the strict sense of a partial acquired lan-

guage disorder, with 'aphasia' referring to complete absence of language. However, this is rarely adhered to strictly.

Aphasias are disturbances of language and not simply motor speech dysfunctions, thus a patient with aphasia will also have impairment of other aspects of language, such as writing. The term 'aphemia' is reserved for patients with impaired speech but with intact writing. 'Dysarthrias' refer to impaired speech sound production, and 'dysphonia' to local disturbances of the larynx and pharynx. Different terms have been used to describe the clinical spectrum of language disturbance. Many of these arose out of the early descriptions of neurologists, which were based on a variety of theoretical constructs, for example conduction, transcortical motor, and transcortical sensory aphasias were terms introduced to describe syndromes based upon theoretical models of language developed by Wernicke and Lichtheim. These models implied precise localization of function with fibre tracts connecting them. These were assumed to have an anatomical basis. Subsequently considerable advances were made in analysing individual components of speech comprehension and production, using information-processing models. The theoretical models and diagrams in these instances relate to individual components of the process without implying any anatomical correlates. However, in some instances the information-processing models can be correlated with the earlier theoretical and neurological models. With improved techniques of neuro-imaging, and particularly the opportunities of functional neuroimaging with activation paradigms on PET scanning, considerable advances in the anatomical correlates of the individual processes in language can be anticipated.

A broad distinction between fluent and non-fluent aphasias is followed here, as this can provide a useful starting point for the clinician, and within this framework the broad distinction between disturbances of production and comprehension are considered. Disturbances of reading, the dyslexias; of writing, the dysgraphias; and of calculation, the dyscalculias, are often associated but are considered separately.

Many of the clinical language syndromes can be identified by simple bedside testing, although detailed neuropsychological assessment is required both for quantitation and careful dissection of the individual components of language failure. Examination should include careful observation of the patient's spontaneous speech, which can be assisted by the use of picture description. The fluency should be noted and the occurrence of paraphasias documented. These may be phonemic paraphasias, in which one or two of the syllables of the word are mistaken or substituted, for example 'stable' for 'table', a pattern more commonly found with anterior lesions. By contrast, semantic paraphasias, the substitution of semantically similar words, for example 'chair' for 'table', are found more commonly with posterior lesions. Comprehension can be tested at the single-word and at the sentence level, and a variety of neuropsychological tests are available for this, such as the Peabody test. For bedside testing, word compre-

hension can be assessed by giving the patient verbal instructions, but care has to be exercised both in patients in whom intellect may be impaired and in patients with dyspraxia, if the task is motor dependent. Individual word comprehension can be tested by verbal definition and confrontational naming, which can also assess word retrieval. Repetition can provide evidence of dissociations between errors in spontaneous speech and repetition, and serves to distinguish the clinical syndromes of conduction aphasias and the transcortical aphasias. Finally, both reading and writing should be assessed.

Aphasias are most commonly encountered in the setting of strokes and neoplasms, i.e. focal lesions, and patients will often have associated neurological signs such as hemiparesis or visual field defects. More difficult to assess are patients with aphasia as part of a more generalized cognitive impairment, such as occurs with degenerative dementias. In addition, patients with psychosis or with acute confusional states can create problems, although the language process itself is preserved if carefully observed. Thus paraphasic errors are rare in the psychoses, although the rare schizophrenic 'word salad' can create diagnostic difficulty. However, other evidence of disturbed behaviour is apparent, whereas the patient with jargon aphasia as part of a Wernicke's dysphasia is seen to behave normally in the realm of non-language behaviour. The mute patient presents a particular diagnostic challenge. Patients may be mute because of a severe dysphasia, but more commonly are anarthric, in which case writing will be preserved. Alternatively, mutism may be associated with disturbances in attention, such as occurs with frontal and subfrontal disease and may be seen in akinetic mutism.

Clearly, any assessment of a patient requires knowledge of handedness. The vast majority of people have language represented in the left hemisphere. Very rarely (less than 1 per cent) of right-handed individuals may develop aphasia with right hemisphere lesions (crossed aphasia in dextrals). In approximately half of patients who are left-handed language also resides in the left hemisphere.

Non-ftuent and Broca's aphasia'

In 1861 Broca described the case of Monsieur Leborgne, who had sustained a stroke with damage to the left inferior frontal gyrus and underlying white matter. The patient was initially mute and was then left with a severe non-fluent aphasia. Broca's original terminology for this, aphemia, has subsequently been confined to patients with impairment of speech but preservation of writing, usually with lesions of the dominant inferior motor cortex. The term aphasia, introduced by Trousseau, supplanted the term aphemia. The striking feature of Broca's aphasia is that the speech is non-fluent, being both slow and reduced in output, and patients are often mute initially. The content of the speech may be impaired, with frequent phonemic errors, and is usually agrammatic, with the omission of prepositions, adjectives, and adverbs. Repetition and confrontation naming (see below) are normally impaired, although the patients are often

helped by cueing. Writing is faulty, both in morphology and in terms of spelling and grammar.

One of the clinically distinguishing features of Broca's aphasia is that the impairment is largely confined to language expression, with relative preservation of comprehension. Indeed, auditory comprehension of individual words is very well preserved, although performance on tests used to explore sentence comprehension is usually impaired; similar subtle impairment of comprehension can be found in reading.

The traditional Broca's area, established in the original cases, is the posterior part of the inferior frontal gyrus. An associated ideomotor apraxia of the non-dominant hand may be found, depending upon the extent of subcortical damage. Some patients will show quite striking dysarthria and associated orofacial dyspraxia.

Two distinct clinical patterns of Broca's aphasia have been described, depending on the size of the lesion. Lesions confined to Broca's area and subcortical white matter are usually due to embolic strokes in the anterior branches of the left middle cerebral artery, and are associated with rapid recovery of expressive speech. Patients with occlusions of the middle cerebral artery, sparing the territory of the inferior division which supplies the temporal lobe, or patients with occlusion of the internal carotid, have a more widespread lesion, which renders them globally aphasic initially, and often unable to comprehend, together with a dense hemiparesis. However, over the subsequent months of recovery, comprehension improves and a residual Broca's aphasia is left.

The majority of patients with Broca's aphasia have suffered strokes, but the syndrome may also be found with tumours, although in a less pure form. Some cases of selective left hemisphere degeneration may also present with a non-fluent speech, as in primary progressive aphasia, and some patients with degeneration of the frontal lobe, such as occurs in Pick's disease, may develop a striking orofacial dyspraxia with speech impairment.

Lichtheim had originally proposed a model of cortical concept centres for words, which were connected with the motor centre or word sound centre by transcortical pathways. Theoretical syndromes based on this model and involving disconnections between the centres were postulated for conduction (see below), transcortical motor and transcortical sensory aphasias. In transcortical motor aphasia, patients make frequent errors of speech production with a very low output and frequent phonemic paraphasias. However, repetition is intact.

Transcortical motor aphasia is seen most commonly with anterior cerebral artery lesions, with an associated ideomotor apraxia of the left hand and a right hemiparesis affecting the leg more than the arm.

By contrast with transcortical motor aphasia, patients with conduction aphasia have a profound impairment of repetition with frequent phonemic paraphasias. This was explained as a disconnection between intact comprehension and intact motor centres which would allow for relatively normal spontane-

ous speech. Anatomically, this was attributed to lesions of the arcuate fasciculus which, indeed, are often associated with conduction aphasias.

Speech production requires the correct selection and ordering of phonemes, impairment of which gives rise to the characteristic phonemic errors seen with a conduction aphasia. A pattern of deficit has also been recognized due to impairment of the motor coordination required for phoneme production, so-called kinetic speech production impairment. This is often associated with lesions in the inferior precentral gyrus. These disturbances of phoneme selection and expression can be distinguished from dysarthrias, in which there are characteristic impairments in swallowing and generation of meaningless sounds, which require the same motor apparatus.

Nominal dysphasia

Intact speech is dependent upon appropriate word retrieval. Patients with impaired word retrieval may be relatively fluent but their speech appears empty with frequent circumlocutions. Clinically this can be tested by confrontational naming, when abnormalities may be apparent, particularly for low-frequency words, that are less obvious in spontaneous speech. Wordfinding difficulties are found quite frequently in neurological practice, but can occur as a relatively isolated finding in patients with left temporal lobe lesions. The study of word retrieval has proved to be a fertile area for theoretical modelling and a number of important clinical observations have been made. First, naming may be modality specific; for example, patients may be unable to name when presented with the object visually but are able to do so when presented to touch, so called optic aphasia. In addition, patients have been described in whom a tactile naming impairment is confined to the left hand, and such cases are most easily interpreted as disconnection syndromes involving lesions of the corpus callosum. Another distinction has been drawn between patients whose failure at naming is consistent, and patients in whom the failure varies between different testing sessions and appears to be sensitive to the precise timing of confrontation. Different names are failed on different occasions and an object may be correctly named, but not if immediately shown again. The latter has been interpreted as an impairment of access to the word store, so called semantic access dysphasia. This syndrome of impaired access can be contrasted with patients in whom confrontational naming is impaired because they have lost their verbal semantic memory; in these instances the same words tend not to be named and patients can quite often verbalize their loss of comprehension.

One of the striking clinical features of word-finding difficulty is the phenomenon of category specificity, namely that certain categories of words are more impaired than others. In some instances, the specificity is so striking as to have been recognized as a distinct syndrome, for example, colour anomia in patients who are unable to name but can adequately match colours; letter naming or letter anomia, and body part naming, or autotopagnosia. Many additional dis-

sociations have been demonstrated, for example, between action naming and object naming, living and inanimate objects, etc. These category-specific dysphasias provide important theoretical insights into language organization and have been proposed to depend upon the association of the word with various attributes at the time meaning is acquired. Thus, for example, words which are associated with a strong visual component, of which colour would be the most striking, can be contrasted with those, such as tools and manipulable objects, which would depend on a major proprioceptive input when the word acquires its meaning. Such an account would accord well with current concepts of parallel distributed processing across neural networks.

Wernicke's aphasia

Shortly after Broca's description, Karl Wernicke outlined the features of a fluent aphasia which, in many respects, provided the clinical counterpart of a Broca's aphasia. The striking feature is that such patients speak fluently but the speech is often empty of meaning with frequent semantic paraphasias. At times the paraphasias may be profound with frequent neologisms, so called jargon aphasia. Comprehension is invariably impaired, as is reading. Writing reflects the language impairment, with frequent semantic paraphasias and spelling errors. Repetition, as with Broca's aphasia, is impaired. Wernicke's aphasia is commonly due to a vascular lesion and the acute onset of a jargon aphasia is usually due to an embolus to the inferior division of the middle cerebral artery. The area involved is the posterior superior temporal gyrus, often extending into the inferior parietal area. By contrast to Broca's aphasia, Wernicke's aphasia is often unaccompanied by neurological deficit on examination, which to the unwary can lead to faulty diagnosis of a psychotic disturbance. A right superior quadrantanopia may be found if carefully sought.

Intact comprehension requires intact speech perception, and patients may be seen with so-called pure word deafness. A number of these patients, with bilateral temporal lobe lesions, have been shown to have impairment of auditory temporal acuity. However, some patients have impairment of phoneme discrimination which can be associated with left temporal lobe lesions.

As the counterpart to transcortical motor aphasia, Lichtheim proposed the syndrome of transcortical sensory aphasia, in which patients are able to repeat, and whose speech is fluent, but is associated with impaired comprehension and paraphasias. The model postulated that the word recognition centre was intact, as shown by an intact repetition, but dissociation from a central meaning system resulted in impaired comprehension. This syndrome is now interpreted as an impairment of verbal semantic memory. It can be seen with posterior border zone infarcts but more commonly in frontotemporal degeneration, where it is the major feature of the clinical syndrome of semantic dementia. Rarely, patients may be seen with isolation of the speech area who are neither able to speak nor to understand, but are able to repeat.

Dysprosody

Patients with Broca's aphasia often have impairment of the normal rhythm of speech, so-called dysprosody. Sometimes this may be so pronounced as to be referred to as the 'foreign accent syndrome'. Impairment of the emotional expression and comprehension of speech is often found with right hemisphere lesions, and attempts have been made to seek comparable dysphasia syndromes to those found with left hemisphere lesions.

Subcortical aphasias

Dysphasias are classically associated with cortical lesions, but subcortical damage is increasingly being recognized as a cause of dysphasia. To some extent these mimic the classical dysphasia syndromes, depending upon their location, for example, anterior lesions resulting in a non-fluent aphasia. In many instances reduced metabolism can be demonstrated on PET scanning in the appropriate cortical area, and is presumed to reflect impaired projection systems. Other syndromes have been described; for example, ischaemic lesions of the head of the caudate nucleus and associated internal capsule present with striking orofacial dyspraxia, dysarthria, and non-fluent dysphasia. Left thalamic haemorrhages frequently give rise to an aphasia, often with fluctuations in arousal with concomitant fluctuation in language function.

Disorders of speech production and dysarthria

Dysarthria as a disorder of articulation does not involve any disturbance in the proper construction and use of words. In the dysarthric patient, symbolic verbal formulation is normal: only the mechanism of verbal sound production is faulty. When so severely affected that the patient is totally unable to articulate, it is referred to as anarthria. Dysphonia is applied to local disturbance of the larynx and may also render the patient mute. As well as structural abnormalities of the larynx, impaired innervation of laryngeal muscles can lead to dysphonia. A 'bovine cough' is a simple clinical sign of inability to close the larynx.

The articulatory muscles on each side appear to be innervated by both cerebral hemispheres. Hence a unilateral corticospinallesion, for example in the internal capsule, may cause temporary but not permanent dysarthria. However, an extensive unilateral lesion involving the motor cortex may cause persistent dysarthria, especially when the dominant hemisphere is involved; in this case the dysarthria is often associated with some degree of Broca's aphasia. However, dysarthria is consistently produced by bilateral corticospinal lesions, due, for example, to congenital diplegia, vascular lesions of both internal capsules, degeneration of both corticospinal tracts (as in motor neuron disease), and lesions such as tumours involving both corticospinal tracts together in the midbrain. With such lesions, the articulatory muscles are weak and spastic and the tongue ap-

pears smaller, firmer, and less mobile than normal. The jaw-jerk and the palatal and pharyngeal reflexes are exaggerated. Speech is slurred and often explosive, production of consonants, especially labials and dentals, being severely affected. Spastic dysarthria is usually associated with dysphagia and often with impairment of voluntary control over emotional expression, the syndrome of 'pseudobulbar palsy'.

With lesions of the corpus striatum, articulation is impaired, partly, at least, as a result of muscular rigidity. Thus in hepatolenticular degeneration and in parkinsonism, articulation is slow and slurred, owing to immobility of the lips and tongue, and the pitch of the voice is monotonous. In the dystonias and Huntington's disease, dysarthria is common; indeed in severe cases speech may be unintelligible. In these diseases irregular respiration may also contribute to the dysarthria.

The co-ordination of articulation suffers severely when the cerebellar vermis is damaged and also when lesions involve the cerebellar connections in the brainstem. Speech in such cases is often explosive, with slurring and undue separation of individual syllables-scanning or syllabic speech. Ataxic dysarthria of this character is seen after acute cerebellar lesions and in multiple sclerosis and the hereditary ataxias.

Lower motor neuron lesions cause wasting and weakness, and often fasciculation, of the muscles of articulation (true bulbar palsy). In the early stages, the pronunciation of labials suffers most. Later, progressive weakness of the tongue impairs the production of dentals and gutterals, and weakness of the soft palate gives the voice a nasal quality. There is often associated dysphonia and finally total anarthria. Motor neuron disease is the most common cause, but paresis of the bulbar muscles may also be seen in syringobulbia, bulbar poliomyelitis, cranial polyneuritis, and brainstem tumours.

Combinations of these varieties of dysarthria are common; for example, in multiple sclerosis the articulatory muscles may be both spastic and ataxic, and in motor neuron disease a combination of upper and lower motor neuron lesions may be present. Diseases of the muscles, such as myasthenia gravis, polymyositis, and muscular dystrophy involving facial muscles, lead to a dysarthria similar to that resulting from lesions of the lower motor neurons. In myasthenia, fatigability may cause increased slurring if the patient is asked to count aloud. In the myotonias, impaired muscular relaxation may add a spastic quality to the speech.

Palilalia

Palilalia is a rare disorder of speech which, as its name implies (from the Greek *palin*, again; *lalein*, to chatter), is characterized by repetition of a phrase which the patient reiterates with increasing rapidity. Palilalia most frequently occurs in postencephalitic parkinsonism, in general paresis, frontotemporal de-

generations, and in pseudobulbar palsy due to vascular lesions. In echolalia the patient repeats or echoes words or brief phrases spoken by the examiner. It is usually seen in frontotemporal degenerations.

Agraphia, alexia, and acalculia

The majority of aphasic syndromes are associated with impairment of writing or dysgraphia. This is such a frequent association clinically that sparing of writing with impaired speech usually indicates that the speech impairment is due to a disruption of speech production rather than a pure dysphasic syndrome. Similarly, some patients may demonstrate dysgraphia with intact speech. Agraphias have been broadly divided into those that affect the processes of spelling and those that affect writing. The latter can be seen as a particular type of ideational dyspraxia, although patients are described in whom praxis is otherwise preserved. Disorders of spelling as such have also been subdivided, and have allowed the generation of theoretical models similar to the informational processing models for reading. Dysgraphias are typically associated with posterior dominant parietal lesions.

Acquired disorders of reading, or dyslexias, are commonly found with dysphasias but can present in isolation. These were originally classified by Dejerine into two broad groups: those with and those without dysgraphia. In clinical terms this distinction has stood the test of time. Dyslexia with dysgraphia is commonly seen with lesions of the left angular gyrus. This type of dyslexia is often seen together with agraphia, acalculia, and anomia, and has been described as a distinct syndrome by Gerstmann, although this is only an observed clustering and each of these is not dependent on the others. In the syndrome of alexia without agraphia, patients are unable to read but are able to write, even though they cannot read their own writing. This is often found with colour anomia, and patients usually have a right hemianopia. It is most commonly seen with lesions of the left parieto-occipital area, often involving the splenium of the corpus callosum. The classical interpretation of this syndrome has been that of a disconnection of visual information in the intact left field from the left angular gyrus. However, this does not explain readily a striking feature of these patients, which is the ability to read using a letter by letter strategy. Information-processing models have now largely replaced the neurological models of reading. Using these models, alexia without agraphia can be interpreted as a word-form dyslexia, supported by the fact that these patients are more impaired on reading script than print. It is argued that following initial word-form recognition, analysis may proceed either by a phonological route or by a sight vocabulary route.

Impairment of arithmetic ability is relatively common and is seen frequently with aphasia. However, it can be recognized as a selective lesion and is found most commonly with left parietal lesions. The dyscalculia commonly arises as a consequence of dyslexia or dysgraphia and so-called spatial acalculia

due to visuospatial disorganization when written arithmetic calculations are performed. Amusia, an inability to produce and appreciate music is seen most commonly with non-dominant hemisphere lesions, although the reading and writing of music notation may be seen with left hemisphere lesions.

DISORDERS OF MEMORY

Memory is the ability to store and subsequently retrieve past experience and is central to many cognitive functions, and the maintenance of an autobiographical memory is central to personal identity.

It is clear that memory is not a unitary function and there is a profusion of different terms. However, it is usual to draw a distinction between short-term (or primary) and long-term (or secondary) memory. Short term, primary, or immediate memory can be tested at the bedside as the digit span. A normal person can usually retain a maximum of seven or eight digits, with rapid forgetting over some 30 seconds unless rehearsed. Although less commonly tested at the bedside, patients may also have a selective impairment of short-term visual memory. The original simple model that memory involved entry into the short-term store before consolidation into a long-term store, secondary memory is no longer tenable, as patients with impaired digit span may have normal learning and secondary memory. Current theories of the role of primary memory range from a component of the working memory model of Baddeley (1986), to involvement in language fluency, or as a safety backup resource. From the neurologist's point of view, reduced digit span is commonly seen with impairment of attention, but as an isolated finding can be related to lesions of the inferior dominant parietal lobe, where it often occurs with dyscalculia.

Disabling memory impairments arise when individuals lose the ability to maintain an autobiographical memory. This can occur in a variety of clinical situations, such as dementia and confusional states, but it is the patients with otherwise intact cognition who have provided the main basis for study. Such patients typically have two components to their impairment: an anterograde amnesia (i.e. a deficit in acquiring new memories following the illness) and a retrograde amnesia (i.e. a loss of recall for events prior to the illness). The patient H.M., who had bilateral medial temporal lobe resections extending back some 8 cm from the temporal poles, has been studied intensively and provided important insights into amnesia. These studies demonstrate a profound impairment of both verbal and non-verbal learning with intact immediate recall, as evidenced by normal digit span (Scoville and Milner 1957; Milner *et al.* 1968). Subsequent similar cases of amnesia have followed this pattern. The status of remote memories has been less secure. Ribot's law states that there is a direct relationship between the strength of a memory and its recency, i.e. old memories being better

preserved, and indeed this is often observed at the bedside. However, there are problems of interpretation since it is difficult to match the saliency of the remembered events. Despite the profound memory loss in H.M. and other similar cases, there is preservation of certain types of learning, for example improved performance on the recognition of fragmented letters can be demonstrated and, most strikingly, a retained ability to acquire new motor skills, often without recollection of having done so.

In the case of H.M., impaired learning of both verbal and visual material was found, but these can be selectively impaired. Group studies indicate that patients with left hemisphere damage have impaired verbal memory and the converse for non-verbal or visual memory. Often these material-specific memory impairments do not present clinically, but rather are found on specific testing. On occasions, however, some do present to the neurologist, the most striking being a topographical memory impairment in patients who are unable to recall familiar routes or buildings.

Studies of amnesia had focused previously on failure at various putative stages of memory, in terms of input, storage, and retrieval. Impairments of input and consolidation suggested that the strength and endurance of a memory depends on the extent of processing and thus consolidation. This interpretation of amnesia in terms of impaired storage had argued that consolidation and retrieval mechanisms were intact, but that there was an increased rate of forgetting. More recently, however, attention has focused on the dissociations between preserved and impaired memory functions, observations which cannot easily be accommodated within a simple unitary model of memory with consolidation and retrieval models. Cohen and Squire (1982) contrasted procedural learning, i.e. 'knowing how', and declarative knowledge, 'knowing that', memory. This describes the situation of patients acquiring new motor skills often without explicit knowledge of having done so. One patient for example, was able to learn a new piano tune without any recollection of having done so, and replay if prompted with the initial bars. However, the dimension of declarative memory does not easily explain the deficits seen in patients such as H.M. in whom memory for words, part of declarative knowledge, is well preserved. There is difference between episodic, i.e. memory for day-to-day events, and semantic memory. Other approaches have looked at the dynamic processes involved rather than observed dichotomies, for example the processes involved in implicit and explicit learning, i.e. those which are variably dependent upon the degree of conscious recall.

A large variety of diseases may be associated with amnesia. Most commonly, memory impairment is seen with confusional states or dementia, but in these instances the amnesia is part of a wider spectrum of cognitive impairment (see below). Diseases affecting the medial temporal lobes and other structures on the limbic circuit may cause amnesia. Thus midline tumours in the region of the third ventricle, such as craniopharyngiomas, colloid cysts, massive pituitary tumours, thalamic gliomas, and tumours of the splenium of the corpus callosum,

believed to be due to involvement of the fornix, can all cause a severe amnesia. Inflammatory disorders, such as sarcoidosis and other granulomatous lesions in the same areas and limbic encephalitis as a paraneoplastic phenomenon, are also associated with amnesia. A profound memory impairment is also commonly seen with herpes encephalitis, due to the selective involvement of the medial temporal cortex. Vascular events of the posterior cerebral artery, which supplies the medial temporal lobe and hippocampus, can cause amnesia. This often occurs with bilateral damage in association with basilar artery syndromes, but can occur with unilateral cerebral artery occlusions, particularly in the elderly, which may be due to pre-existing contralateral hippocampal damage.

The Korsakoff syndrome is a striking amnesia which usually follows a Wernicke's encephalopathy. Patients present with a profound amnesia and are quite unable to remember events even within the last half an hour, but may be shown to have implicit learning, of motor skills for example. Other tests of cognitive function are well preserved in the pure form of Korsakoff's syndrome, but in clinical practice a spectrum may be seen, with the more generalized cognitive impairment of alcoholic dementia at one end and patients with a pure Korsakoff syndrome at the other. It is, however, the striking contrast between the profound amnesia and the relatively minor additional cognitive defects that characterizes Korsakoff's syndrome. There is often striking confabulation, when a patient may provide imaginary accounts of his actions to create what, at times, can be a plausible autobiographical memory.

Transient loss of memory is also a common clinical problem with both anterograde and retrograde amnesia, the latter shrinking on recovery, leaving a gap in memory for the period of anterograde memory impairment subsequent to the onset. Temporary memory loss may occur with a variety of conditions which result in either generalized cerebral dysfunction or with selective disturbance of the medial temporal lobe and diencephalon. These include epilepsy, most commonly temporal lobe epilepsy, and in some patients there may be no obvious disturbance of consciousness. Cerebral tumours may cause episodic memory loss which may also be on an epileptic basis. Head injury, drugs, especially alcohol, and benzodiazepines are common causes. Transient memory impairment may also occur as a feature of transient ischaemic episodes in posterior cerebral territory. A picture resembling transient global amnesia may also occur with migraine but this is usually with a clinical history of previous migraine attacks and the episodes are normally followed by headache. Psychogenic amnesia and hysterical fugue states, a not infrequent topic of newspaper stories, are discussed below.

Transient global amnesia

This is a striking syndrome affecting the middle aged and the elderly. The history is obtained of sudden onset of impairment of episodic or autobiographi-

cal memory. The attacks are frequently reported to have been triggered by sexual intercourse or sudden cold, winter bathing in the elderly being a classic history. The attacks last from 1-24 hours and the patients may repeatedly ask questions and appear anxious, but otherwise able to drive home, and there have been reports of virtuoso musical performances during an attack. Investigations are usually normal and a full recovery can be anticipated, although some patients are left with mild memory impairment. Recurrences are rare but do occur in a small proportion. A vascular cause may underlie the syndrome of transient global amnesia, although supportive evidence has been difficult to establish and epidemiological studies have suggested a closer link to migraine.

Paramnesias

Confabulation, the production of memories without any basis in real events, can accompany amnesia and is most commonly observed in Korsakoff's syndrome. However, confabulation can be seen in patients with adequate performance on routine memory testing and is therefore more appropriately considered as a paramnesia. Two classes of confabulation have been distinguished. Momentary or provoked confabulation occurs in response to questions and requests for specific information that the patient might reasonably be expected to know. More florid is fantastic confabulation, in which the patient will spontaneously produce bizarre accounts, often far in excess of what might be required in response to the situation. Confabulation is found most commonly in association with frontal-lobe lesions, particularly in medial frontal-lobe lesions.

Reduplicative paramnesia describes a behavioural disturbance in which the patient transposes or reduplicates places. For example he might claim that his home is not his normal home but a very similar building in which he is staying, or alternatively that the hospital in which he has been admitted is in his home town. Such patients usually have bifrontal or right frontal lesions. A similar syndrome is the Capgras syndrome in which patients refuse to recognize people, often close relatives who are familiar to them, claiming them to be impostors. The Capgras syndrome is usually seen in association with right hemisphere lesions.

DEMENTIA & AMNESTIC SYNDROMES

DEMENTIA

Dementia refers to an acquired, generalized, and often progressive impairment of cognitive function that affects the content, but not the level, of consciousness. Although its incidence increases with advancing age (it has been estimated to affect 5-20% of individuals over age 65), dementia is not an invariable accompaniment of aging. It reflects instead an underlying pathology that affects the cerebral cortex, its subcortical connections, or both.

Minor changes in neurologic function, including alterations in memory and other cognitive spheres, are associated with normal aging. Enlargement of ventricles and cerebral cortical sulci seen on CT or MRI scans is also common with normal aging. These findings should not by themselves be considered indicative of dementia.

Neurologic changes in normal aging

Cognitive
- Memory loss (benign senescent forgetfulness)

Neuro-ophthalmologic
- Small, sluggishly reactive pupils
- Impaired upgaze
- Impaired convergence

Motor
- Muscular atrophy (intrinsic hand and foot muscles)
- Increased muscle tone
- Flexion (stooped) posture
- Gait disorders (small-stepped or broad-based gait)

Sensory
- Impaired vision
- Impaired hearing
- Impaired taste
- Impaired olfaction
- Decreased vibration sense

Reflexes
- Primitive reflexes
- Absent abdominal reflexes
- Absent ankle jerks

The first step in evaluating a patient with a disorder of cognitive function is to classify the disorder as either a disturbance of the level of consciousness (wakefulness or arousal), such as an acute confusional state or coma, or a disturbance of the content of consciousness, in which wakefulness is preserved. The latter category includes both global cognitive disorders (dementia) and more circumscribed deficits, such as aphasia and amnestic syndromes. This distinction is important because the initial classification of the disorder determines the subsequent diagnostic approach. The most common problem in this area is distinguishing dementia from an acute confusional state, such as that produced by drug intoxication. Another common problem is differentiating between dementia and so-called pseudodementia, such as that produced by depression.

An important goal in clinical evaluation of patients with suspected dementia is to find the cause. Although only about 10% of dementias are reversible, the possibility of reversing or arresting the disorder through appropriate treatment and dramatically improving the quality and duration of life justifies a thorough diagnostic investigation. A diagnosis is important in other cases for purposes of providing a prognosis, genetic counseling, or alerting family members and medical personnel to the risk of a transmissible disease. As better treatments are developed for dementing disorders that are unresponsive or poorly responsive to current therapy, the importance of arriving at an etiological diagnosis of dementia will continue to increase.

Since dementia implies deterioration in cognitive ability, it is important to establish that the patient's previous level of functioning has declined. Data that can help to establish the cause of dementia include the time course of deterioration; associated symptoms such as headache, gait disturbance, or incontinence; family history of a similar condition; concurrent medical illnesses; and the use of alcohol and prescribed or unprescribed drugs.

The general physical examination can contribute to the etiologic diagnosis when it reveals signs of a systemic disease responsible for the dementia.

The mental status examination helps to determine whether it is the level or the content of consciousness that is impaired and whether the cognitive dysfunction is global or circumscribed. A disorder of the level of consciousness is suggested by sleepiness, inattention, impairment of immediate recall, or disorientation as to place or time. Abnormalities in these areas are unusual in dementia until the disorder is far advanced.

To determine the scope of the cognitive dysfunction (global or circumscribed), various spheres of cognition are tested in turn. These include memory, language, parietal lobe functions (pictorial construction, right-left discrimination, localization of objects in space), and frontal lobe or diffuse cerebral cortical functions (judgment, abstraction, thought content, the ability to perform previously learned acts). Multiple areas of cognitive function are impaired in dementia. Certain disorders that produce dementia also affect vision, coordination,

or motor or sensory function. Detecting such associated neurologic abnormalities can help to establish an etiologic diagnosis.

DIFFERENTIAL DIAGNOSIS

Common Causes of Dementia

Although a wide variety of diseases can produce dementia, it is generally agreed that Alzheimer's disease is by far the most common cause. Dementia with Lewy bodies has been recognized in recent years as a distinct entity, rather than simply the concurrence of Alzheimer's disease and Parkinson's disease, and may be second in frequency to Alzheimer's disease as a cause of dementia. Vascular dementia, sometimes referred to as multiinfarct dementia, is the next most common. Other causes of dementia, including reversible dementias, are comparatively rare.

Treatable Causes of Dementia

Treatable causes of dementia – such as normal pressure hydrocephalus, intracranial mass lesions, vitamin B12 deficiency, hypothyroidism, and neurosyphilis – are rare. They are important disorders to diagnose promptly, however, because treatment can arrest or reverse the intellectual decline.

Other Important Causes of Dementia

Recognizing that the dementia is caused by Huntington's disease allows patients with this disorder (and their families) to benefit from genetic counseling. If Creutzfeldt-Jakob disease or AIDS dementia complex is diagnosed, precautions can be instituted against transmission; the course of AIDS dementia complex may also be modified by antiviral treatment. Progressive multifocal encephalopathy may indicate underlying immunosuppression that is due to human immunodeficiency virus (HIV) infection, lymphoma, leukemia, or another disorder.

Controversial Causes of Dementia

Some disorders to which dementia is often attributed may not directly cause the disorder. For example, the existence of a primary alcoholic dementia is questionable, since dementia in alcoholic patients may be the result of such related problems as head trauma or nutritional deficiency.

Pseudodementias

About 15% of patients referred for evaluation of possible dementia instead have other disorders (pseudodementias), such as depression. Drug intoxication, commonly cited as a cause of dementia in the elderly, actually produces an acute confusional state, rather than dementia.

ALZHEIMER'S DISEASE

General Considerations

Alzheimer's disease, by far the single most frequent cause of dementia, becomes increasingly common with advancing age and has an equal incidence in both sexes. A slowly progressive disorder of unknown cause that cannot be diagnosed with certainty on clinical grounds, it is characterized by typical histopathologic features: neurofibrillary tangles, neuritic plaques, and granulovacuolar degeneration. Pick's disease, a closely related dementing process in which atrophy is most conspicuous in the frontal and temporal lobes, may be clinically indistinguishable from Alzheimer's disease. Although a distinction was formerly made between presenile Alzheimer's disease and senile dementia of the Alzheimer type, these conditions appear to be clinically and pathologicall y identical.

Pathogenesis

A. Genetic. Alzheimer's disease is usually sporadic, but a genetic basis can be identified in some cases. Patients with trisomy 21 (Down's syndrome), which is usually due to the presence of three free copies of chromosome 21 but can also result from translocation of the third copy to chromosome 14 or 21, have a high incidence of Alzheimer's disease beginning in the fourth decade. Familial Alzheimer's disease with autosomal dominant inheritance has also been documented and is genetically heterogeneous. In some families there are associated mutations in the gene for amyloid precursor protein on chromosome 21. These are missense mutations that result from single amino acid substitutions, producing a protein with altered function. In other kindreds, familial Alzheimer's disease has an especially early onset and more virulent course and is linked to mutations in the gene for presenilin 1, a membrane protein, on chromosome 14. Mutations in another transmembrane protein, presenilin 2, have been associated with familial Alzheimer's disease in a German kindred. Some cases of familial Alzheimer's disease are not caused by these defects, and mutations at other sites are presumed responsible. Genetic factors may also modify susceptibility to Alzheimer's disease without being directly causal: in late-onset familial (and to a lesser extent sporadic) Alzheimer's disease, the risk of being affected and the age at onset are related to the number of other apolipoprotein E (APOE4) alleles on chromosome 19. How the APOE4 allele (or the absence of APOE alleles) confers disease susceptibility is unclear. It has been speculated that apolipoprotein E produced by astrocytes may be taken up into neurons and interact abnormally with microtubule-associated proteins, like tau, to produce paired helical filaments in neurofibrillary tangles.

B. Role of β-amyloid. Amyloid β-protein (13amyloid or Aβ) is deposited in neuritic plaques (as their principal constituent) and in cerebral and meningeal blood vessels of patients with Alzheimer's disease. In addition, some cases of familial Alzheimer's disease are associated with mutations affecting the amyloid precursor protein. These findings suggest that alterations in the metabolism of amyloid precursor protein (APP) to β-amyloid may be involved in the pathogenesis of Alzheimer's disease. In Down's syndrome, the extra copy of chromosome 21, which codes for APP, would be expected to cause increased production of APP and its product, β-amyloid. Missense mutations in the APP gene alter the enzymatic cleavage of APP, resulting in increased production of a long, 42-amino-acid form of β-amyloid that may be especially likely to form amyloid fibrils. Missense mutations in the presenilin genes are also associated with abnormal processing of APP. Finally, apolipoprotein E may interact with β-amyloid. These observations are consistent with, but do not prove, a unifying role for β-amyloid in the genetic forms of Alzheimer's disease identified to date. β-Amyloid – especially its aggregated form – can also be toxic to neurons in vitro under some circumstances. It has therefore been suggested that the abnormal accumulation of β-amyloid in Alzheimer's disease is responsible for the death of selectively vulnerable neurons. However, others have cited the lack of a clear correlation between the extent of amyloid deposition in the brain and the severity of dementia as evidence against the amyloid hypothesis.

C. Neurochemical. Changes in several neurotransmitter and neuromodulator systems have been found in the brains of patients dying of Alzheimer's disease; whatever the underlying cause of the disorder, these changes may contribute to its clinical expression. The acetylcholine-synthesizing enzyme choline acetyltransferase is markedly depleted in the cerebral cortex and hippocampus of patients with Alzheimer's disease. Degeneration of the nucleus basalis of Meynert (the principal origin of cortical cholinergic innervation) and of the cholinergic septal-hippocampal tract may underlie this abnormality. Several neurotransmitters (acetylcholine, somatostatin, vasopressin, β-endorphin, corticotropin, substance P) are depleted in the brains of patients with Alzheimer's disease, perhaps as a result of the selective loss of certain neuronal populations.

D. Toxic. A role has been proposed for aluminum toxicity in the pathogenesis of Alzheimer's disease. This is based on findings that the concentration of aluminum in the brain increases with age, and aluminum is present in the neurofibrillary tangles and neuritic plaques of brains from patients with Alzheimer's disease. In addition, aluminum-containing dialysates may be responsible for a dementia associated with chronic hemodialysis (see Dialysis Dementia, below). It is, however, unlikely that exposure to aluminum in antacids, drinking water, or cooking utensils increases the risk of developing Alzheimer's disease.

Endogenous excitotoxins, eg, the amino acid neurotransmitters glutamate and aspartate, may contribute to neuronal death in Alzheimer's disease, but this hypothesis is unproven.

E. Infectious. No infectious agent has been identified in Alzheimer's disease.

Clinical Findings

A. Early Manifestations. Impairment of recent memory is typically the first sign of Alzheimer's disease – often noticed only by family members. As the memory disorder progresses, the patient becomes disoriented to time and then to place. Aphasia, anomia, and acalculia may develop, forcing the patient to leave work or give up the management of family finances. The depression apparent in the earlier stages of the disorder may give way to an agitated, restless state. Apraxias and visuospatial disorientation ensue, causing the patient to become lost easily. Primitive reflexes are commonly found. A frontal lobe gait disorder may become apparent, with short, slow, shuffling steps, flexed posture, wide base, and difficulty in initiating walking.

B. Late Manifestations. In the late stages, previously preserved social graces are lost, and psychiatric symptoms, including psychosis with paranoia, hallucinations, or delusions, may be prominent. Seizures occur in some cases. Examination at this stage may show extrapyramidal rigidity and bradykinesia. Rare and usually late features of the disease include myoclonus, incontinence, spasticity, extensor plantar responses, and hemiparesis. Mutism, incontinence, and a bedridden state are terminal manifestations, and death typically occurs from 5 to 10 years after the onset of symptoms.

Investigative Studies

Laboratory investigations do not assist in the diagnosis – except to exclude other disorders. The CT scan or MRI often shows cortical atrophy and enlarged ventricles, but such changes may also be seen in elderly nondemented patients.

Differential Diagnosis

A. Early Dementia. Alzheimer's disease must be distinguished from depression and from such pure disorders of memory as the Korsakoff amnestic syndrome associated with chronic alcoholism.

B. More Advanced Dementia. Multi-infarct dementia and Creutzfeldt-Jakob disease must often be considered.

1. Multi-infarct dementia is suggested by a stepwise progression of deficits, pseudobulbar palsy, or focal sensorimotor abnormalities.

2. Creutzfeldt-Jakob disease is characterized by a shorter course than Alzheimer's disease (often leading to death within 1 year), prominent myoclonus, cerebellar dysfunction, more frequent pyramidal and extrapyramidal signs, visual disturbances, and a characteristic electroencephalographic pattern of periodic complexes.

Treatment

No currently available treatment has been shown unequivocally to revers existing deficits or arrest the disease's progression. Because cholinergic neuronal pathways degenerate and choline acetyltransferase is depleted in the brains of patients with Alzheimer's disease, cholinergic replacement therapy has been used in an effort at symptomatic treatment of cognitive dysfunction. The drugs tried have included acetylcholine precursors (choline, lecithin), drugs that stimulate acetylcholine release (piracetam, 4aminopyridine), acetylcholinesterase inhibitors (tacrine, donepezil), and muscarinic cholinergic receptor agonists (arecholine). Of these, tacrine and donepezil have been shown in some studies to improve cognitive function. Their effects are modest and their long-term efficacy is unproven, however, and reversible hepatotoxicity is common with tacrine. Therefore, liver enzymes (especially alanine aminotransferase) must be monitored at frequent intervals. Several other pharmacologic treatments have been proposed for cognitive dysfunction in Alzheimer's disease, including cerebral vasodilators (papaverine, dihydroergotoxine), central nervous system stimulants (amphetamines, pentylenetetrazol, procainamide), opioid antagonists (naloxone), and neuropeptides (vasopressin), but none has proved helpful. Antipsychotic drugs, antidepressants, and anxiolytics may be useful for controlling behavioral disturbances.

Prognosis

Early in the course of the disease, patients can usually remain at home and continue social, recreational, and limited professional activities. Early diagnosis can allow patients time to plan orderly retirement from work, to arrange for management of their finances, and to discuss with the physician and family members the management of future medical problems. Patients in advanced stages of the disease may require care in a nursing facility and the use of psychoactive medications. These patients must be protected and prevented from injuring themselves and their families by injudicious actions or decisions. Death from inanition or infection generally occurs 5-10 years after the first symptoms.

PICK'S DISEASE

Pick's disease is one of a group of idiopathic neurodegenerative disorders that produces a syndrome sometimes referred to as frontotemporal dementia. These disorders may be distinguished from Alzheimer's disease by their generally earlier onset, more prominent behavioral than cognitive dysfunction at presentation, and preferential atrophy of the frontal and anterior temporal lobes on CT scan or MRI of the brain. However, definitive diagnosis is usually not possible during life, and relies instead on histopathological features. These include the distinctively circumscribed pattern of lobar atrophy, the presence of Pick

cells and Pick inclusion bodies, and the absence of amyloid plaque and neurofibrillary tangles characteristic of Alzheimer's disease. Familial occurrence of Pick's disease and of other frontotemporal dementias has been documented. In some kindreds with frontotemporal dementia, the gene defect has been mapped to chomosome 17 (17q21). There is no treatment.

CREUTZFELDT-JAKOB DISEASE

Creutzfeldt-Jakob disease is an invariably fatal transmissible disorder of the central nervous system and is characterized by rapidly progressive dementia and variable focal involvement of the cerebral cortex, basal ganglia, cerebellum, brain stem, and spinal cord. A proteinaceous infectious particle (prion) has been proposed as the etiologic agent, and prion proteins can be demonstrated by immunohistologic methods in the brains of patients with Creutzfeldt-Jakob disease. Familial cases have been associated with mutations in a form of the prion protein (cellular isoform, or PrP^{c}), which is expressed by normal neurons but whose function is unknown. In sporadic cases, an abnormal prion protein (scrapie isoform, or PrP^{sc}), which differs from PrP^{c} in its secondary (folding) structure, has been proposed as the infectious agent. In both circumstances, the result is accumulation of abnormal PrP^{sc} prions in brain tissue. To explain the ability of PrP^{sc} prions to replicate in the brain (despite the fact that they contain no detectable nucleic acids), it has been suggested that infectious PrP^{sc} prions induce a conformational change in normally expressed PrP^{sc} prions that converts them to the PrP^{sc} form. Prions have also been implicated in three other rare disorders – kuru, a dementing disease of Fore-speaking tribes of New Guinea (apparently spread by cannibalism); Gerstmann-Straussler syndrome, a familial disorder characterized by dementia and ataxia; and fatal familial insomnia, which produces disturbances of sleep and of autonomic, motor, and endocrine function.

While transmission from humans to animals has been demonstrated experimentally, documented human-to-human transmission (by corneal transplantation, cortical electrode implantation, or administration of human growth hormone) is rare. The infectious agent is present in the brain, spinal cord, eyes, lungs, lymph nodes, kidneys, spleen, liver, and CSF, but not other body fluids. Conjugal cases are rare and do not necessarily imply spouse-to-spouse transmission. The annual incidence of Creutzfeldt-Jakob disease is about 1: 1,000,000 population. The naturally acquired disease occurs in patients 16-82 years of age, with a peak incidence between 60 and 64 years and an equal sex incidence. More than one member of a family is affected in 5-10% of cases.

Clinical Findings

The clinical picture may be that of a diffuse central nervous system disorder or of a more localized dysfunction. Dementia is present in virtually all cases

and may begin as a mild global cognitive impairment or a focal cortical disorder such as aphasia, apraxia, or agnosia. Progression to akinetic mutism or coma typically ensues over a period of months. Psychiatric symptoms including anxiety, euphoria, depression, labile affect, delusions, hallucinations, and changes in personality or behavior may be prominent.

Aside from cognitive abnormalities, the most frequent clinical manifestations are myoclonus (often induced by a startle), extrapyramidal signs (rigidity, bradykinesia, tremor, dystonia, chorea, or athetosis), cerebellar signs, and extrapyramidal signs. Visual field defects, cranial nerve palsies, and seizures occur less often.

A clinically and pathologically distinct new variant of Creutzfeldt-Jakob disease has been described and is thought to result from the transmission of bovine spongiform encephalopathy to humans. This variant is characterized by an earlier onset (mean age, about 30 years), a more prolonged course (median duration over I year), and prominent early psychiatric abnormalities, including depression and personality changes.

Investigative Studies

The EEG may show a typical but nonspecific pattern of periodic sharp waves or spikes. CSF protein may be mildly elevated (<100 mg/dL). Definitive diagnosis is by immunoblot detection of PrP^{sc} in brain tissue obtained at biopsy or, in familial cases, by detection of mutant forms of PrP^{c} in DNA from lymphocytes.

Differential Diagnosis

A variety of other disorders must be distinguished from Creutzfeld-Jakob disease. Alzheimer's disease is often a consideration, especially in patients with a less fulminant course and a paucity of cerebellar and extrapyramidal signs. Where subcortical involvement is prominent, Parkinson's disease, cerebellar degeneration, or progressive supranuclear palsy may be suspected. Striking focal signs raise the possibility of an intracerebral mass lesion. Acute metabolic disorders that produce altered mentation and myoclonus (eg, sedative drug withdrawal) can mimic Creutzfeldt-Jakob disease.

Prognosis

No treatment is currently available. The disease is usually relentlessly progressive and, although transient improvement may occur, invariably fatal. In most sporadic cases, death occurs within 1 year after the onset of symptoms: the mean duration of illness in these patients is 7 months. Depending on the specific mutation present, familial forms of the disease may have similar short or much longer courses.

NORMAL-PRESSURE HYDROCEPHALUS

Normal-pressure hydrocephalus, a potentially reversible cause of dementia, is characterized by the clinical triad of dementia, gait apraxia, and incontinence. It may be idiopathic or secondary to conditions that interfere with cerebrospinal fluid absorption, such as meningitis or subarachnoid hemorrhage. The dementia is often mild and insidious in onset, and is typically preceded by the gait disorder and incontinence. It is characterized initially by mental slowness and apathy and subsequently by global cognitive dysfunction. Deterioration of memory is common, but focal cognitive disorders such as aphasia and agnosia are rare.

Pathophysiology

Normal-pressure hydrocephalus is sometimes called communicating (because the lateral, third, and fourth ventricles remain in communication) or nonobstructive hydrocephalus (because the flow of CSF between the ventricles is not obstructed). It is presumed to be due to impaired CSF absorption from arachnoid granulations in the subarachnoid space over the convexity of the hemispheres, eg, from meningeal fibrosis and adhesions following meningitis or subarachnoid hemorrhage. In contrast, noncommunicating or obstructive hydrocephalus is caused by a blockade of CSF circulation within the ventricular system (eg, by an intraventricular cyst or tumor) and is associated with increased CSF pressure and often with headache and papilledema.

Clinical Findings

Normal-pressure hydrocephalus usually develops over a period of weeks to months; a gait disorder is often the initial manifestation. This typically takes the form of gait apraxia, characterized by unsteadiness on standing and difficulty in initiating walking even though there is no weakness or ataxia. The patient can perform the leg movements associated with walking, bicycling, or kicking a ball and can trace figures with the feet while lying or sitting but is unable to do so when the legs are bearing weight. The patient typically appears to be glued to the floor, and walking, once under way, is slow and shuffling.

Pyramidal signs, including spasticity, hyperreflexia, and extensor plantar responses, are sometimes present. Motor perseveration (the inappropriate repetition of motor activity) and grasp reflexes in the hands and feet may occur. Urinary incontinence is a later development, and patients may be unaware of it; fecal incontinence is uncommon.

Investigative Studies

Lumbar puncture reveals normal or low opening pressure. The CT scan or MRI typically shows enlarged lateral ventricles without increased prominence of

cortical sulci. Radionuclide cisternography classically shows isotope accumulation in the ventricles, delayed clearance, and failure of ascent over the cerebral convexities. This pattern is not necessarily present in patients who respond to shunting, however. Transient improvement in gait, cognitive testing, or sphincteric function following the removal of 30-50 mL of CSF by lumbar puncture is probably the best predictor of a favorable clinical response to shunting (see below).

Differential Diagnosis

A variety of conditions that produce dementia must be considered in the differential diagnosis. Alzheimer's disease tends to follow a longer course, often with prominent focal cortical dysfunction and enlarged cortical sulci shown in a CT scan or MRI. Parkinsonism may be simulated by the gait disorder but can be distinguished by extrapyramidal rigidity, tremor, and response to anti parkinsonian medications. Multi-infarct dementia should be suspected if the disorder follows a stepwise course, or pseudobulbar palsy, focal sensorimotor signs, or a history of stroke are encountered.

Treatment

Some patients, especially those with hydrocephalus from meningitis or subarachnoid hemolThage, recover or improve following ventriculoatrial, ventriculoperitoneal, or lumboperitoneal shunting. In idiopathic normal-pressure hydrocephalus, about one-half of patients have sustained improvement and about one-third have a good or excellent response (ie return to work) after shunting. As noted above, a favorable response to the removal of CSF by lumbar puncture may be the best predictor of successful surgery. Complications of shunting occur in about one-third of patients and include shunt infection, subdural hematoma, and shunt malfunction that necessitates replacement.

DEMENTIA WITH LEWY BODIES

Up to one-fourth of elderly demented patients who come to autopsy have round, eosinophilic, intracytoplasmic neuronal inclusions (Lewy bodies) in the cerebral cortex and brainstem. Dementia with Lewy bodies is found in patients with (Lewy-body variant of Alzheimer's disease) and without (diffuse Lewy-body disease) histopathological features of Alzheimer's disease, and is probably a heterogeneous disorder. In contrast to Alzheimer's disease, it is characterized clinically by cognitive decline without prominent early memory impairment. Other distinctive features include fluctuating cognitive ability, well-formed visual hallucinations, and signs of parkinsonism, especially rigidity and bradykinesia. These patients may respond well to anticholinesterase drugs such as tacrine or donepezil, but are especially sensitive to extrapyramidal side effects of antipsychotic drugs, which should therefore be avoided or used with caution.

ALCOHOLISM

Several complications of alcoholism are known to cause dementia. These include acquired hepatocerebral degeneration as a result of alcoholic liver disease, chronic subdural hematoma from head trauma, and certain rare disorders resulting from nutritional deficiency.

Pellagra, caused by deficiency of nicotinic acid (niacin), affects neurons in the cerebral cortex, basal ganglia, brainstem, cerebellum, and anterior horns of the spinal cord. Systemic involvement is manifested by diarrhea, glossitis, anemia, and erythematous skin lesions. Neurologic involvement may produce dementia; psychosis; confusional states; pyramidal, extrapyramidal, and cerebellar signs; polyneuropathy; and optic neuropathy. Treatment is with nicotinamide, but the neurologic deficits may persist despite treatment.

Marchiafava Bignami syndrome is characterized by necrosis of the corpus callosum and subcortical white matter and occurs most often in malnourished alcoholics. The course can be acute, subacute, or chronic. Clinical features include dementia, spasticity, dysarthria, gait disorder, and coma. The diagnosis can sometimes be made by CT scan or MRI. No specific treatment is available, but cessation of drinking and improvement of nutrition are advised. The outcome is variable: patients may die, survive with dementia, or recover.

The Korsakoff amnestic syndrome is a common and well-recognized cause of cognitive dysfunction in malnourished alcoholic patients. Because this disorder produces selective impairment of memory rather than global cognitive dysfunction, it is discussed in the section on amnestic syndromes (below).

It has been proposed that dementia can occur as a direct result of the toxic effects of ethanol on the brain, but this is disputed, and no distinctive corresponding abnormalities have been identified in the brains of demented alcoholics. Therefore, alcoholism should not be considered an adequate explanation for dementia, at least until other causes – especially those that are treatable – have been investigated and excluded.

HYPOTHYROIDISM

Hypothyroidism (myxedema) can also produce a reversible dementia or chronic organic psychosis. The dementia is a global disorder characterized by mental slowness, memory loss, and irritability. Focal cortical deficits do not occur. Psychiatric manifestations are typically prominent and include depression, paranoia, visual and auditory hallucinations, mania, and suicidal behavior.

Associated neurologic symptoms and signs may be helpful in pointing to hypothyroidism as the cause of dementia. The most suggestive finding in this regard is delayed relaxation of the tendon reflexes. Patients with myxedema may

complain of headache, hearing loss, tinnitus, vertigo, weakness, or paresthesia. Examination may show deafness, dysarthria, or cerebellar ataxia.

The diagnosis of myxedema is based upon the laboratory finding of decreased blood levels of T_4 and T_3, usually associated with increased TSH. Cognitive dysfunction is usually reversible with treatment.

VITAMIN B_{12} DEFICIENCY

Vitamin B_{12} deficiency is a rare cause of reversible dementia and organic psychosis. Like the acute confusional state associated with vitamin B_{12} deficiency, such syndromes can occur with or without hematologic and other neurologic manifestations.

The dementia consists of global cognitive dysfunction with mental slowness, impaired concentration, and memory disturbance; aphasia and other focal cortical disorders do not occur. Psychiatric manifestations are often prominent and include depression, mania, and paranoid psychosis with visual and auditory hallucinations.

DIALYSIS DEMENTIA

A subacute progressive – and ultimately fatal – dementia is an uncommon accompaniment of chronic hemodialysis; the mean duration of hemodialysis at the onset of the symptom is about 3 years. The neurologic symptoms are prominent dysarthria (often the earliest feature), multifocal myoclonus, and generalized or occasionally partial motor seizures. The symptoms are initially intermittent, being maximal following dialysis; they later become permanent, and dementia supervenes. The mean survival time in established cases is 6 months.

The interictal EEG is invariably abnormal, showing paroxysmal high-voltage slowing with intermixed spikes and slow waves. The CSF examination is normal. Brain CT studies show diffuse atrophy.

The ability of diazepam to reverse the clinical electroencephalographic features of dialysis dementia suggests an epileptic component to the disorder. Aluminum in the dialysate is a major etiologic suspect, since elevated aluminum levels have been found in the brains of patients with dialysis dementia, and removing trace metals from the dialysate has markedly decreased the syndrome's incidence. Reports of the therapeutic effectiveness of renal transplantation have been conflicting.

NON-WILSONIAN HEPATOCEREBRAL DEGENERATION

Acquired (non-Wilsonian) hepatocerebral degeneration is an uncommon complication of chronic hepatic cirrhosis with spontaneous or surgical portosystemic shunting. The mechanisms underlying cerebral symptoms are unclear but

may be related to failure of the liver to detoxify ammonia. Neurologic symptoms precede hepatic symptoms in about one-sixth of patients.

Systemic manifestations of chronic liver disease are usually present. The neurologic syndrome is characterized by a fluctuating but generally progressive course over 1-9 years, often punctuated by bouts of acute hepatic encephalopathy. Dementia, dysarthria, and a variety of cerebellar, extrapyramidal, and pyramidal signs are the most common manifestations. Dementia is marked by mental slowness, apathy, impaired attention and concentration, and memory disturbance. The patient appears alert, in contrast to the somnolence or delirium seen in acute hepatic encephalopathy.

Cerebellar signs include gait and limb ataxia and dysarthria; nystagmus is rare. Extrapyramidal involvement may produce rigidity, resting tremor, dystonia, chorea, or athetosis. Adventitious movements tend to be most marked in the head, face, and neck. Asterixis, intention or action myoclonus, hyperreflexia, and extensor plantar responses are common findings; paraparesis occurs rarely.

Because episodes of acute hepatic encephalopathy may be superimposed on the chronic neurologic disorder, it may be difficult to determine the relative contributions of acute and chronic syndromes to the clinical state of the patient. The diagnosis of acute hepatic encephalopathy is suggested by somnolence or agitated delirium, acute neurologic deterioration, or ongoing gastrointestinal bleeding.

Laboratory studies show abnormal hepatic blood chemistries and elevated blood ammonia, but the degree of abnormality bears no direct relationship to the severity of neurologic symptoms. The CSF is normal, except for increased glutamine and an occasional mild elevation of protein.

Several disorders resemble acquired hepatocerebral degeneration, but they can be distinguished by clinical or laboratory features. In Wilson's disease, the onset is typically earlier, and neurologic involvement often precedes hepatic involvement. Kayser-Fleischer rings and laboratory evidence of abnormal copper metabolism are present, but there is no episodic encephalopathy. The ataxia of alcoholic cerebellar degeneration primarily affects gait rather than causing limb ataxia and dysarthria.

Patients may benefit from a low-protein diet, lactulose, neomycin, liver transplantation, or portosystemic shunting. Shunting may also precipitate or worsen neurologic symptoms, however. Improvement following levodopa or bromocriptine therapy has been described. Death ultimately results from progressive hepatic failure or variceal bleeding.

TRAUMA

Severe open or closed head injury, particularly when followed by a prolonged period of unconsciousness, may cause posttraumatic syndromes with impaired memory and concentration, personality changes, headache, focal neu-

rologic disorders, or seizures. Cognitive impairment is nonprogressive, and the cause is usually obvious.

A syndrome of delayed and progressive posttraumatic dementia following repeated head injury (dementia pugilistica) has been described in boxers. It may begin-and typically continues to progressyears after the episodes of trauma have ceased. Dementia is characterized by cheerful or labile affect, mental slowness, memory deficit, and irritability. Associated neurologic abnormalities include tremor, rigidity, bradykinesia, dysarthria, cerebellar ataxia, pyramidal signs, and seizures. Neuroradiologic investigations may show cortical atrophy and cavum septi pellucidi.

VASCULAR DEMENTIA

Vascular dementia is the second or third most common cause of dementia, after Alzheimer's disease, and perhaps dementia with Lewy bodies. Most patients with this diagnosis have either multiple large cortical infarcts from occlusion of major cerebral arteries or several smaller infarcts (lacunar state) affecting subcortical white matter, basal ganglia, or thalamus. However, the relationship between cerebral vascular disease and dementia has been defined only vaguely. Thus, the precise number of strokes, their locations, and the total infarct volume required for strokes to produce dementia are uncertain, making it difficult sometimes to know whether strokes are the cause of dementia or are unrelated. Whether dementia can result from cerebrovascular disease without frank infarction, as is commonly presumed to exist when periventricular white matter lesions are detected by neuroimaging, is also controversial. Thus, the absence of neuroradiologic signs of cerebrovascular disease argues strongly against a vascular basis for dementia, but the presence of vascular lesions does not prove that they are causal. This is especially true when another cause of dementia, such as Alzheimer's disease, coexists with cerebrovascular disease.

As classically described, patients with multi-infarct dementia have a history of hypertension, a stepwise progression of deficits, a more or less abrupt onset of dementia, and focal neurologic symptoms or signs.

Because extensive pathologic changes may already exist at presentation, it is assumed that patients can remain functionally well compensated until a new and perhaps otherwise innocuous infarct tips the balance.

The neurologic examination commonly shows pseudobulbar palsy with dysarthria, dysphagia, and pathologic emotionality (pseudobulbar affect), focal motor and sensory deficits, ataxia, gait apraxia, hyperreflexia, and extensor plantar responses.

The MRI may show multiple small subcortical lucencies. Extensive areas of low density in subcortical white matter are seen in Binswanger's disease (subcortical arteriosclerotic encephalopathy), which may be a related condition. MRI is more sensitive than CT for detecting these abnormalities. Additional labora-

tory studies should be performed to exclude cardiac emboli, polycythemia, thrombocytosis, cerebral vasculitis, and meningovascular syphilis as causes of multiple infarctions, particularly in younger patients or those without a history of hypertension.

Hypertension, when present, should be treated to reduce the incidence of subsequent infarction and to prevent other end-organ diseases.

PSEUDODEMENTIA

Depression is the disorder most commonly mistaken for dementia. Because depression is common and usually treatable, distinguishing between the two conditions is of obvious clinical importance.

Both dementia and the pseudodementia of depression can be characterized by mental slowness, apathy, self-neglect, withdrawal, irritability, difficulty with memory and concentration, and changes in behavior and personality. In addition, depression can be a feature of most dementing illnesses, and the two disorders frequently coexist. If depression is identified as a significant problem and is not correctable by treatment of an underlying disease or by a change in medication, it should be treated directly. Modes of treatment include psychotherapy, tricyclic and related antidepressants, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, and electroconvulsive therapy.

AMNESTIC SYNDROMES

A disorder of memory (amnestic syndrome) may occur as one feature of an acute confusional state or dementia or as an isolated abnormality. Memory is a complex function that can be viewed as comprising phases of registration, storage, and retrieval. Autopsy and MRI studies of the brains of patients with memory disorders suggest that the hippocampus and related structures, such as the dorsomedial nucleus of the thalamus, are important in memory processing. Bilateral damage to these regions results in impairment of short-term memory, which is manifested clinically by the inability to form new memories. Long-term memory, which involves retrieval of previously learned information, is relatively preserved, perhaps because well established memories are stored diffusely in the cerebral cortex. Some patients with amnestic syndromes may attempt to fill in gaps in memory with false recollections (confabulation), which can take the form of elaborate contrivances or of genuine memories misplaced in time. The longest-standing and most deeply ingrained memories, however, such as one's own name, are almost always spared in organic memory disturbances. In contrast, such personal memories may be prominently or exclusively impaired in dissociative (psychogenic) amnesia.

The cellular basis of memory is poorly understood, but repetitive neuronal firing produces lasting pre- and postsynaptic changes that facilitate neurotransmission at hippocampal synapses (long-term potentiation). These changes appear to involve the release of glutamate, which stimulates the entry of calcium into postsynaptic neurons and the production of a retrograde chemical messenger (perhaps nitric oxide) that acts on presynaptic nerve terminals to increase transmitter release upon subsequent firing.

Causes of amnestic syndromes

Acute

- Accompanying acute confusional states
- Head trauma
- Hypoxia or ischemia
- Bilateral posterior cerebral artery occlusion
- Transient global amnesia
- Alcoholic blackouts
- Wernicke's encephalopathy
- Dissociative (psychogenic) amnesia

Chronic

- Accompanying dementias
- Alcoholic Korsakoff amnestic syndrome
- Postencephalitic amnesia
- Brain tumor
- Paraneoplastic limbic encephalitits

HEAD TRAUMA

Head injuries resulting in loss of consciousness are invariably associated with an amnestic syndrome. Patients seen shortly after such an injury exhibit a confusional state in which they are unable to incorporate new memories (anterograde, or posttraumatic amnesia, although they may behave in an apparently normal automatic fashion. In addition, retrograde amnesia is present, covering a variable period prior to the trauma. Features characteristic of transient global amnesia (see below) may be seen.

As full consciousness returns, the ability to form new memories is restored. Events occurring in the confusional interval tend to be permanently lost to memory, however. Exceptions are islands of memory, for a lucid interval between trauma and unconsciousness, or for periods of lesser impairment in the course of a fluctuating posttraumatic confusional state. The period of retrograde amnesia begins to shrink, with the most remote memories the first to return. The

severity of the injury tends to correlate with the duration of confusion and with the extent of permanent retrograde and posttraumatic amnesia.

HYPOXIA OR ISCHEMIA

Because of the selective vulnerability of pyramidal neurons in the Sommer sector (hi sector of Scholz) of the hippocampus, conditions resulting in cerebral hypoxia or ischemia, such as cardiac arrest or carbon monoxide poisoning, can produce amnestic syndromes. Amnesia tends to occur in patients in whom coma has lasted at least 12 hours. There is severe impairment of the ability to incorporate new memories, with relative preservation of registration and remote memory; patients typically appear to have an isolated disorder of short-term memory. A period of retrograde amnesia preceding the insult may occur. Patients exhibit a lack of concern about their impairment and sometimes confabulate. Amnesia following cardiac arrest may be the sole manifestation of neurologic dysfunction, or it may coexist with other cerebral watershed syndromes, such as bibrachial paresis, cortical blindness, or visual agnosia. Recovery often occurs within several days, although deficits may persist.

Amnestic syndromes from carbon monoxide poisoning are frequently associated with affective disturbances. Other associated abnormalities include focal cortical and extrapyramidal dysfunction. Acute carbon monoxide poisoning is suggested by cherryred coloration of the skin and mucous membranes, elevated carboxyhemoglobin levels, or cardiac arrhythmia. The CT brain scan may show lucencies in the basal ganglia and dentate nuclei.

BILATERAL POSTERIOR CEREBRAL ARTERY OCCLUSION

The posterior cerebral artery supplies the medial temporal lobe, thalamus, posterior internal capsule, and occipital cortex. Ischemia or infarction in this territory, typically when bilateral, may produce a transient or permanent amnestic syndrome. Emboli in the vertebrobasilar system are frequent causes of such disorders.

The amnestic syndrome is usually associated with unilateral or bilateral hemianopia and sometimes with visual agnosia, alexia without agraphia, anomia, sensory disturbances, or signs of upper midbrain dysfunction (especially impaired pupillary light reflex). Recent memory tends to be selectively impaired, with relative preservation of remote memory and registration.

The CT scan shows lucencies – which may or may not be enhanced by use of contrast material – in any combination of the above-mentioned regions.

TRANSIENT GLOBAL AMNESIA

Transient global amnesia is a syndrome of acute memory loss that tends to occur in middle-aged or elderly patients with risk factors for atherosclerotic disease, especially a prior ischemic event in the posterior cerebral circulation. The disorder is recurrent in fewer than 10% of patients.

A primary disorder of short-term memory that can last for minutes or days, it typically lasts for hours. Patients appear agitated and perplexed and may repeatedly inquire about their whereabouts, the time, and the nature of what they are experiencing. Knowledge of personal identity is preserved, as are remote memories and registration. New memories cannot be formed, however, which accounts for the patient's repetitive questions. Retrograde amnesia for a variable period preceding the episode may be present, but this period shrinks as the episode resolves.

The patient's obvious concern about the condition distinguishes transient global amnesia from most other organically based amnestic syndromes and may give rise to the suspicion that amnesia is psychogenic. A CT scan or MRI may demonstrate focal thalamic or temporal lobe abnormalities. Recently, diffusion-weighted MRI has shown signal abnormalities in the temporal lobe during spells of transient global amnesia. These are compatible with cellular edema and may be related to spreading depression a wave of cellular depolarization accompanied by cellular swelling in the brain.

ALCOHOLIC BLACKOUTS

Short-term consumption of large amounts of ethanol by alcoholic or non-alcoholic individuals may lead to "blackouts"-transient amnestic episodes that are not due to global confusion, seizures, head trauma, or the Wernicke-Korsakoff syndrome. These spells are characterized by an inability to form new memories, without impairment of longterm memory or immediate recall. Although the cause is unknown, alcoholic blackouts may result from ethanol-induced depression of synaptic (especially serotonin- or glutamate-mediated) neurotransmission. The disorder is self-limited and no specific treatment is required, but reduction of the ethanol intake should be counseled, and thiamine should be given to treat possible Wernicke's encephalopathy.

WERNICKE'S ENCEPHALOPATHY

Wernicke's encephalopathy is caused by thiamine deficiency and classically produces an acute confusional state, ataxia, and ophthalmoplegia. Amnesia

may be the major or sole cognitive disturbance, however, especially after thiamine treatment is begun and other cognitive abnormalities improve.

DISSOCIATIVE (PSYCHOGENIC) AMNESIA

Amnesia may be a manifestation of a dissociative disorder or of malingering. In such patients a prior psychiatric history, additional psychiatric symptoms, or a precipitating emotional stress can often be identified.

Dissociative amnesia is characterized by an isolated or a disproportionate loss of traumatic or stressful personal memories. Dissociative amnesia is usually localized in time to the immediate aftermath of a traumatic experience or selective for some but not other events during such a period. Less frequent patterns include systematized amnesia restricted to certain categories of information, continuous amnesia for events from some time in the past up to and including the present, and generalized amnesia. In some cases, the patient may be unable to remember even his own name – an exceedingly rare finding in organic amnesia. Despite such disorientation to person, orientation to place and time may be preserved. In addition, recent memories may be less affected than remote memories-the reverse of the pattern customarily seen in amnesia caused by organic disease. Examination under hypnosis or after administration of barbiturates may be helpful in establishing that amnesia is of psychogenic origin.

ALCOHOLIC KORSAKOFF AMNESTIC SYNDROME

The Korsakoff amnestic syndrome, which occurs in chronic alcoholism and other malnourished states, is thought to be caused by thiamine deficiency. It is usually preceded by one or more episodes of Wernicke's encephalopathy, but such a history may be lacking. The memory disorder may be related to bilateral degeneration of the dorsomedial thalamic nuclei.

An amnestic syndrome of variable severity follows recovery from Wernicke's encephalopathy in about three-fourths of cases and is often associated with polyneuropathy and other residua such as nystagmus or gait ataxia. The essential defect is an inability to form new memories, resulting in significant impairment of short-term memory. Long-term memory is also frequently affected, although to a lesser extent. Registration is intact. Patients are typically apathetic and lack insight into their disorder. They may attempt to reassure the physician that no impairment exists and try to explain away their obvious inability to remember. Confabulation is often, but not invariably, a feature.

Korsakoff s syndrome can be prevented or its severity decreased by prompt administration of thiamine to patients with Wernicke's encephalopathy. Patients with established Korsakoff s syndrome should also receive thiamine to

prevent the progression of deficits, although existing deficits are unlikely to be reversed.

POSTENCEPHALITIC AMNESIA

Patients who recover from acute viral encephalitis – particularly that caused by herpes simplex virus – may be left with a permanent and static amnestic syndrome. The syndrome is similar to that produced by chronic alcoholism in that an inability to form new memories is its outstanding feature. Remote memories are affected to a lesser extent than are recent ones, and registration is intact. Confabulation may occur. Often there is total amnesia for the period of the acute encephalitis. Patients may also exhibit other symptoms of limbic system disease. These include docility, indifference, flatness of mood and affect, inappropriate jocularity and sexual allusions, hyperphagia, impotence, repetitive stereotyped motor activity, and the absence of goal-oriented activity. Complex partial seizures, with or without secondary generalization, may occur.

BRAIN TUMOR

Brain tumor is a rare cause of amnestic syndrome. Tumors that can present in this manner include those that are located in the third ventricle or that compress its floor or walls from without. The amnestic syndrome closely resembles that of Korsakoffs syndrome. In addition, patients with deep midline tumors often exhibit marked lethargy, headache, endocrine disturbances, visual field deficits, or papilledema. The diagnosis of brain tumor is made by CT scan or MRI. Treatment consists of surgery or irradiation or both, depending upon the type of tumor and its location.

PARANEOPLASTIC LIMBIC ENCEPHALITIS

An inflammatory and degenerative disorder of gray matter regions of the central nervous system can occur as a remote effect of systemic cancer. When limbic structures are primarily affected, the clinical picture is that of an amnestic syndrome. The cause is not known, but as in other paraneoplastic neurologic syndromes, anti neuronal autoantibodies may be involved. Paraneoplastic limbic encephalitis is most often associated with small cell cancer of the lung, and symptoms typically precede diagnosis of the underlying cancer. Histopathologic findings include neuronal loss, reactive gliosis, microglial proliferation, and perivascular lymphocytic cuffing. Gray matter of the hippocampus, cingulum, piriform cortex, inferior frontal lobes, insula, and amygdala is characteristically

affected. Symptoms develop over several weeks. The disorder is characterized by profound impairment of recent memory, corresponding to the inability to learn new material. Remote memory is less impaired, and registration is unaffected; confabulation occurs in some cases. Affective symptoms, either anxiety or depression, are common early features. Hallucinations and complex partial or generalized seizures may occur. In many instances, the amnestic syndrome progresses to a global dementia.

Depending upon the extent to which gray matter regions outside the limbic system are involved, cerebellar, pyramidal, bulbar, and peripheral nerve disturbances may coexist with the amnestic disorder.

The CSF may show a modest mononuclear pleocytosis and mildly elevated protein. Diffuse slowing or bitemporal slow waves and spikes are sometimes seen on EEG. An MRI may reveal abnormal signal intensity in the medial temporal lobes.

The paraneoplastic amnestic syndrome can be static, it can progress, or it can remit. Because no specific treatment is available, excluding treatable disorders is of primary importance. Korsakoff s syndrome caused by thiamine deficiency should especially be considered, because patients with cancer are susceptible to nutritional deficiency and thiamine administration may prevent these symptoms from worsening.

COMA

Coma is a sleeplike state in which the patient makes no purposeful response to the environment and from which he or she cannot be aroused. The eyes are typically closed and do not open spontaneously. The patient does not speak, and there is no purposeful movement of the face or limbs. Verbal stimulation produces no response. Mechanical (eg, painful) stimulation may also produce no response or may elicit nonpurposeful reflex movements mediated through spinal cord or brainstem pathways. Coma results from a disturbance in the function of either the brainstem reticular activating system above the midpons or both cerebral hemispheres, since these are the brain regions that maintain consciousness.

The approach to diagnosis of the comatose patient consists first of emergency measures to stabilize the patient and treat presumptively certain life-threatening disorders, followed by efforts to establish an etiologic diagnosis.

EMERGENCY MANAGEMENT

1. Ensure patency of the airway and adequacy of ventilation and circulation. This is accomplished by rapid visual inspection and by measuring the vital signs. If the **airway** is obstructed, the obstruction should be cleared and the patient intubated. If there is evidence of trauma that may have affected the cervical spine, however, the neck should not be moved until this possibility has been excluded by x-rays of the cervical spine. In this case, if intubation is required, it should be performed by tracheostomy. Adequacy of **ventilation** can be established by the absence of cyanosis, a respiratory rate 8/min, the presence of breath sounds on auscultation of the chest, and the results of arterial blood gas and pH studies (see below). If any of these suggest inadequate ventilation, the patient should be ventilated mechanically. Measurement of the pulse and blood pressure provides a rapid assessment of the status of the **circulation**. Circulatory embarrassment should be treated with intravenous fluid replacement, pressors, and antiarrhythmic drugs, as indicated.

2. Insert an intravenous catheter and withdraw blood for laboratory studies. These studies should include measurement of serum glucose and electrolytes, hepatic and renal function tests, prothrombin time, partial thromboplastin time, and a complete blood count. Extra tubes of blood should also be obtained for additional studies that may be useful in certain cases, such as drug screens, and for tests that become necessary as diagnostic evaluation proceeds.

3. Begin an intravenous infusion and administer dextrose, thiamine, and naloxone. Every comatose patient should be given 25 g of dextrose intravenously, typically as 50 mL of a 50% dextrose solution, to treat possible hypoglycemic coma. Since administration of dextrose alone may precipitate or worsen Wernicke's encephalopathy in thiamine-deficient patients, all comatose patients should also receive 100 mg of thiamine by the intravenous route. To treat possible opiate overdose, the opiate antagonist naloxone, 0.4-1.2 mg intravenously, should also be administered routinely to comatose patients. The benzodiazepine antagonist flumazenil should not be used in coma of unknown cause.

4. Withdraw arterial blood for blood gas and pH determinations. In addition to assisting in the assessment of ventilatory status, these studies can provide clues to metabolic causes of coma.

5. Institute treatment for seizures, if present. Persistent or recurrent seizures in a comatose patient should be considered to represent status epilepticus and treated accordingly.

After these measures have been taken, the history (if available) is obtained and general physical and neurologic examinations are performed.

EXAMINATION

History

The most crucial aspect of the history is the time over which coma develops. In the absence of precise details about the mode of onset, information about when the patient was last seen in an apparently normal state may assist in establishing the time course of the disease process.

A. A sudden onset of coma suggests a vascular origin, especially a brainstem stroke or subarachnoid hemorrhage.

B. Rapid progression from hemispheric signs, such as hemiparesis, hemisensory deficit, or aphasia, to coma within minutes to hours is characteristic of intracerebral hemorrhage.

C. A more protracted course leading to coma (days to a week or more) is seen with tumor, abscess, or chronic subdural hematoma.

D. Coma preceded by a confusional state or agitated delirium, without lateralizing signs or symptoms, is probably due to a metabolic derangement.

General Physical Examination

A. Signs of Trauma

1. Inspection of the head may reveal signs of basilar skull fracture, including the following:

a. Raccoon eyes (Periorbital ecchymoses).

b. Battle's sign (Swelling and discoloration overlying the mastoid bone behind the ear).

c. Hemotympanum (Blood behind the tympanic membrane).

d. Cerebrospinal fluid rhinorrhea or otorrhea (Leakage of CSF from the nose or ear). CSF rhinorrhea must be distinguished from other causes of rhinorrhea, such as allergic rhinitis. It has been suggested that CSF can be distinguished from nasal mucus by the higher glucose content of CSF, but this is not always the case. The chloride level may be more useful, since CSF chloride concentrations are 15-20 meq/L higher than those in mucus.

2. Palpation of the head may demonstrate a depressed skull fracture or swelling of soft tissues at the site of trauma.

B. Blood Pressure. Elevation of blood pressure in a comatose patient may reflect long-standing hypertension, which predisposes to intracerebral hemorrhage or stroke. In the rare condition of hypertensive encephalopathy, the blood pressure is above 250/150 mm Hg in chronically hypertensive patients; it may be lower following acute elevation of blood pressure in previously normotensive patients (eg, in acute renal failure). Elevation of blood pressure may also be a consequence of the process causing the coma, as in intracerebral or subarachnoid hemorrhage or, rarely, brainstem stroke.

C. Temperature. Hypothermia can occur in coma caused by ethanol or sedative drug intoxication, hypoglycemia, Wernicke's encephalopathy, hepatic encephalopathy, and myxedema. Coma with hyperthermia is seen in heat stroke, status epilepticus, malignant hyperthermia related to inhalational anesthetics, anticholinergic drug intoxication, pontine hemorrhage, and certain hypothalamic lesions.

D. Signs of Meningeal Irritation. Signs of meningeal irritation (eg, nuchal rigidity or the Brudzinski sign are of great importance in leading to the prompt diagnosis of meningitis or subarachnoid hemorrhage, but they are lost in deep coma.

E. Optic Fundi. Examination of the optic fundi may reveal papilledema or retinal hemorrhages compatible with chronic or acute hypertension or an elevation in intracranial pressure. Subhyaloid (superficial retinal) hemorrhages in an adult strongly suggest subarachnoid hemorrhage.

Neurologic Examination

The neurologic examination is the key to etiological diagnosis in the comatose patient. Pupillary size and reactivity, oculocephalic and oculovestibular reflexes, and the motor response to pain should be evaluated in detail.

A. Pupils

1. Normal pupils. Normal pupils are 3-4 mm in diameter and equal bilaterally; they constrict briskly and symmetrically in response to light. Normal pupils, however, are larger in children and smaller in the old.

2. Thalamic pupils. Slightly smaller reactive pupils are present in the early stages of thalamic compression from mass lesions, perhaps because of the interruption of the descending sympathetic pathways.

3. Fixed dilated pupils. Pupils greater than 7 mm in diameter and fixed (nonreactive to light) usually result from compression of the oculomotor (III) cranial nerve anywhere along its course from the midbrain to the orbit but may also be seen in anticholinergic or sympathomimetic drug intoxication. The most common cause of a fixed dilated pupil in a comatose patient is transtentorial herniation of the medial temporal lobe from a supratentorial mass.

4. Fixed midsized pupils. Pupils fixed at about 5 mm in diameter are the result of brainstem damage at the midbrain level.

5. Pinpoint pupils. Pinpoint pupils (1-1.5 mm in diameter) in a comatose patient usually indicate opioid overdose or focal damage at the pontine level. Under these conditions, the pupils may appear unreactive to light except, perhaps, with a magnifying glass. Pinpoint pupils are also caused by organophosphate poisoning, miotic eye drops, or neurosyphilis.

6. Asymmetric pupils. Asymmetry of pupillary size (anisocoria) with a difference of 1 mm or less in diameter is a normal finding in 20% of the population; the pupils constrict to a similar extent in response to light, and extraocular movements are not impaired. In contrast, a pupil that constricts less rapidly or to a lesser extent than its fellow usually implies a structural lesion affecting the midbrain or oculomotor nerve.

B. Extraocular Movements

1. Pathways tested. The neuronal pathways to be tested begin at the pontomedullary junction (vestibular [VIII] nerve and nucleus), synapse in the caudal pons (horizontal gaze center and abducens [VI] nerve nucleus), ascend through the central core of the brainstem reticular activating system (medial longitudinal fasciculus), and arrive at the midbrain level (oculomotor [III] nucleus and nerve).

2. Methods of testing. In the comatose patient, eye movements are tested by stimulating the vestibular system (semicircular canals of the middle ear) by means of passive head rotation (the oculocephalic reflex, or doll's-head maneuver) or by the stronger stimulus of ice-water irrigation against the tympanic membrane (oculovestibular reflex, or cold-water calories testing).

3. Normal movements. A comatose patient without brainstem disease will often demonstrate full conjugate horizontal eye movements during the doll's-head maneuver and always exhibits tonic conjugate movement of both eyes to the side of the ice water irrigation during caloric testing. The presence of full reflex eye movements in the comatose patient attests to the integrity of the brainstem from the pontine to the midbrain level and excludes a mass lesion in the brainstem.

4. Abnormal movements

a. With lesions of the oculomotor nerve or nucleus (such as in the rostral-caudal herniation syndrome), oculovestibular testing will reveal failure of ocular adduction with unimpaired contralateral abduction.

b. Complete absence of response on oculovestibular testing in a comatose patient implies either a structural lesion of the brainstem at the level of the pons or a metabolic disorder with a particular predilection for brain stem involvement; this is usually caused by sedative drug intoxication.

c. Downward deviation of one or both eyes in response to unilateral cold-water irrigation is most suggestive of sedative drug intoxication.

C. Motor Response to Pain. The motor response to pain is tested by applying strong pressure on the supraorbital ridge, sternum, or nail beds. The response to such stimuli may be helpful in localizing the level of cerebral dysfunction in comatose patients or providing a guide to the depth of coma.

1. With cerebral dysfunction of only moderate severity, patients may localize the offending stimulus by reaching toward the site of stimulation. Although semi purposeful localizing responses to pain can sometimes be difficult to distinguish from the reflex responses described below, movements that involve limb abduction are virtually never reflexive in nature.

2. A decorticate response to pain (flexion of the arm at the elbow, adduction at the shoulder, and extension of the leg and ankle) is classically associated with lesions that involve the thalamus directly or large hemispheric masses that compress it from above.

3. A decerebrate response (extension at the elbow, internal rotation at the shoulder and forearm, and leg extension) tends to occur when midbrain function is compromised. Decerebrate posturing generally implies more severe brain dysfunction than decorticate posturing, but neither response localizes the site of disease precisely.

4. Bilateral symmetric posturing may be seen in both structural and metabolic disorders.

5. Unilateral or asymmetric posturing suggests structural disease in the contralateral cerebral hemisphere or brainstem.

6. In patients with pontine and medullary lesions, there is usually no response to pain, but occasionally some flexion at the knee is noted (a spinal reflex).

PATHOPHYSIOLOGIC ASSESSMENT

The most important step in evaluating the comatose patient is to decide whether unconsciousness is the result of a structural brain lesion (for which emergency neurosurgical intervention may be critical) or a diffuse encephalopathy caused by metabolic disturbance, meningitis, or seizures (for which surgical procedures are unnecessary and medical treatment may be required). The most

common diagnostic dilemma is to try to differentiate between a supratentorial (hemispheric) mass lesion and metabolic encephalopathy.

Supratentorial Structural Lesions

When coma is the result of a supratentorial mass lesion, the history and physical findings early in the course usually point to a hemispheric disorder. Hemiparesis with hemisensory loss is typical. Aphasia occurs with dominant (usually left) hemispheric lesions, and agnosia (indifference to or denial of the deficit) with injury to the non dominant hemisphere. As the mass expands (commonly from associated edema), somnolence supervenes because of the compression of the contralateral hemisphere or downward pressure on the diencephalon. Stupor progresses to coma, but the findings often remain asymmetric. As rostral-caudal compression progresses, the thalamus, midbrain, pons, and medulla become involved, and the neurologic examination reveals dysfunction at successively lower anatomical levels. Such segmental involvement strongly supports the diagnosis of a supratentorial mass with downward transtentorial herniation and dictates the need for neurosurgical intervention. Once the pontine level is reached, a fatal outcome is inevitable. Even at the fully developed midbrain level, chances of survival without severe neurologic impairment decrease rapidly, especially in adults.

When supratentorial mass lesions produce herniation of the medial portion of the temporal lobe (the uncus) across the cerebellar tentorium, thus exerting direct pressure on the rostral brainstem, signs of oculomotor nerve and midbrain compression such as ipsilateral pupillary dilatation and impaired adduction of the eye (uncal syndrome) may precede loss of consciousness. As consciousness is lost with progressive uncal herniation, the fully developed midbrain stage rapidly appears, with marked ipsilateral pupillary dilation and loss of reactivity to light. Neurosurgical treatment must be given early in the course of third-nerve involvement if useful recovery is to be achieved.

Subtentorial Structural Lesions

Coma of sudden onset with focal brainstem signs strongly supports a diagnosis of subtentorial structural lesion. Pupillary function and extraocular movements are the most helpful features of the neurologic examination, especially if the abnormalities are asymmetric. With focal midbrain lesions, pupillary function is lost: the pupils are midsized (about 5 mm in diameter) and nonreactive to light. Pinpoint pupils are found in pontine hemorrhage and less often in pontine infarction or pontine compression caused by cerebellar hemorrhage or infarction. Conjugate gaze deviation away from the side of the lesion and toward the hemiparesis – or disconjugate eye movements, such as internuclear ophthalmoplegia (selective impairment of eye adduction) – strongly suggests a subtentorial lesion. Motor responses are generally not helpful in separating subtentorial from supratentorial lesions. Ventilatory patterns associated with subtentorial le-

sions are abnormal but variable and may be ataxic or gasping. Since the fully developed syndrome of transtentorial herniation from a supratentorial mass is characterized by extensive brainstem dysfunction, its differentiation from a primary subtentorial process may be impossible except by history.

Diffuse Encephalopathies

Diffuse encephalopathies that result in coma (sometimes termed metabolic coma) include not only metabolic disorders such as hypoglycemia and drug intoxication but other processes that affect the brain diffusely, such as meningitis, subarachnoid hemorrhage, and seizures.

The clinical presentation is distinct from that of a mass lesion. There are usually no focal signs, such as hemiparesis, hemisensory loss, or aphasia, and---except in some cases of subarachnoid hemorrhage-no sudden loss of consciousness. Instead, the history reveals a period of progressive somnolence or toxic delirium followed by gradual descent into a stuporous and finally comatose state.

A symmetric neurologic examination supports a metabolic cause of coma. Hepatic encephalopathy, hypoglycemia, and hyperosmolar nonketotic hyperglycemia may uncommonly be accompanied by focal signs – especially hemiparesis, which may alternate from side to side. Asterixis, myoclonus, and tremor preceding coma are important clues that suggest metabolic disease. Symmetric decorticate or decerebrate posturing can be seen with hepatic, uremic, anoxic, hypoglycemic, or sedative-drug-induced coma.

The finding of reactive pupils in the presence of otherwise impaired brainstem function is the hallmark of metabolic encephalopathy. Although coma with intact pupillary reactivity is also seen in the early stages of transtentorial herniation, this latter syndrome is associated with asymmetric neurologic findings. The few metabolic causes of coma that also impair pupillary reflexes include glutethimide overdose, massive barbiturate overdose with apnea and hypotension, acute anoxia, marked hypothermia, and anticholinergic poisoning (large pupils); and opioid overdose (pinpoint pupils). Even in these conditions, however, completely nonreactive pupils are uncommon.

The respiratory patterns in metabolic coma vary widely, and measurement of arterial blood gases and pH may provide a further basis for establishing an etiologic diagnosis.

Summary

Examining pupillary size and reactivity and testing reflex eye movements and the motor response to pain help determine whether brain function is disrupted at a discrete anatomic level (structural lesion) or in a diffuse manner (metabolic coma).

Supratentorial structural lesions compromise the brain in an orderly way, producing dysfunction at progressively lower anatomic levels. In patients with metabolic coma, such localization is not possible, and scattered, anatomically

inconsistent findings are noted on examination. An impressive example of the anatomically discordant findings characteristic of metabolic encephalopathy is the retention of pupillary reactivity in the face of otherwise depressed brainstem functions: paralysis of eye movements, respiratory depression, flaccid muscle tone, and unresponsiveness to painful stimuli such as is typical with sedative drug overdose. The same degree of low brainstem dysfunction produced by a supratentorial mass lesion would have to first compromise the more rostrally situated midbrain structures that mediate pupillary reactivity before affecting the lower brainstem centers.

DIFFERENTIAL DIAGNOSIS

1. PSYCHOGENIC UNRESPONSIVENESS

Psychogenic unresponsiveness is a diagnosis of exclusion that should be made only on the basis of compelling evidence. It may be a manifestation of schizophrenia (catatonic type), somatoform disorders (conversion disorder or somatization disorder), or malingering. The general physical examination reveals no abnormalities; neurologic examination generally reveals symmetrically decreased muscle tone, normal reflexes, and a normal (flexor) response to plantar stimulation. The pupils are 2-3 mm in diameter or occasionally larger and respond briskly to light. Lateral eye movements on oculocephalic (doll's head) testing mayor may not be present, since visual fixation can suppress this reflex. The slow conjugate roving eye movements of metabolic coma cannot be imitated, however, and, if present, are incompatible with a diagnosis of psychogenic unresponsiveness. Likewise, the slow, often asymmetric and incomplete eye closure commonly seen after the eyes of a comatose patient are passively opened cannot be voluntarily reproduced. The patient with psychogenic unresponsiveness usually exhibits some voluntary muscle tone in the eyelids during passive eye opening. A helpful diagnostic test is irrigation of the tympanic membrane with cold water. Brisk nystagmus is the characteristic response in conscious patients, whereas no nystagmus occurs in coma. The EEG in psychogenic unresponsiveness is that of a normal awake person.

2. VEGETATIVE STATE

Some patients who are comatose because of cerebral hypoxia or ischemia- or structural brain lesions – regain wakefulness but not awareness. After 1 month, this condition is termed persistent vegetative state. Such patients exhibit spontaneous eye opening and sleep-wake cycles, which distinguish them from patients in coma, as well as intact brainstem and autonomic function. However,

they neither comprehend nor produce language, and they make no purposeful motor responses. This condition may persist for years. Recovery of consciousness from nontraumatic causes is rare after 3 months, and from traumatic causes is rare after 12 months.

3. LOCKED-IN SYNDROME

Because the portion of the reticular formation responsible for consciousness lies above the level of the midpons, functional transection of the brainstem below this level – by pontine infarct, hemorrhage, central pontine myelinolysis, tumor, or encephalitis – can interrupt descending neural pathways to produce an akinetic and mute state, with preserved consciousness. Such patients appear comatose but are awake and alert although mute and quadriplegic. Decerebrate posturing or flexor spasms may be seen. The diagnosis is made by noting that voluntary eye opening, vertical eye movements, ocular convergence, or some combination of these midbrain-mediated movements is preserved. During the examination of any apparently comatose patient, the patient should be told to "open your eyes," "look up," "look down," and "look at the tip of your nose" to elicit such movements. The EEG is normal. Outcome is variable and related to the underlying cause and the extent of the brainstem lesion. Mortality is approximately 70% when the cause is a vascular disturbance and about 40% in nonvascular cases, usually from pneumonia. Survivors may recover partially or completely over a period of weeks to months.

BRAIN DEATH

Current standards for the determination of brain death, developed by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, are summarized below. Irreversible cessation of all brain function is required for a diagnosis of brain death. In addition, the diagnosis of brain death in children under 5 years of age must be made with caution.

Cessation of Brain Function

A. Unresponsiveness. The patient must be unresponsive to sensory input, including pain and speech.

B. Absent Brainstem Reflexes. Pupillary, corneal, and oropharyngeal responses are absent, and attempts to elicit eye movements with the oculocephalic and vestibulo-ocular maneuvers are unsuccessful. Respiratory responses are also absent, with no ventilatory effort after the patient's PCO_2 is permitted to rise to 60 mm Hg, while oxygenation is maintained by giving 100% oxygen by a cannula inserted into the endotracheal tube (apnea test).

Irreversibility of Brain Dysfunction

The cause of coma must be known; it must be adequate to explain the clinical picture, and it must be irreversible. Sedative drug intoxication, hypothermia (32.2 °C), neuromuscular blockade, and shock must be ruled out, since these conditions can produce a clinical picture that resembles brain death but in which neurologic recovery may still be possible.

Persistence of Brain Dysfunction

The criteria for brain death described above must persist for an appropriate length of time, as follows:

1. Six hours with a confirmatory isoelectric (flat) EEG, performed according to the technical standards.

2. Twelve hours without a confirmatory isoelectric EEG.

3. Twenty-four hours for anoxic brain injury without a confirmatory isoelectric EEG.

INTRACRANIAL PRESSURE, CEREBRAL OEDEMA, HYDROCEPHALUS

RAISED INTRACRANIAL PRESSURE

Pathophysiology

Intracranial pressure (ICP) may become pathologically elevated from diffuse swelling of the brain (cerebral oedema or venous congestion), hydrocephalus, or from other intracranial spaceoccupying lesions, including tumours, haematoma, or abscess. The brain is unique among the viscera in being confined within the rigid case, the cranium. The total volume of the intracranial contents, namely the brain and its coverings, the blood vessels, and the blood and CSF is normally constant, so that an expansion of anyone of these can only occur at the expense of the others. However, the intracranial contents do not respond passively to changes in their volume or pressure, but react in a number of complicated ways, depending mainly on the rate at which they expand.

As an intracranial mass lesion increases in size, there is initially a compensatory reduction in the volume of intracranial blood and CSF and, only when this compensatory process is exhausted, does the intracranial pressure increase. This compensation is best when the rate of expansion is very slow. In this first, or compensated, stage there is little change in the clinical condition of the patient but, in the second stage, as the compensatory process becomes increasingly ineffective, headache and a depressed level of consciousness develop. The third stage of increasing intracranial pressure is characterized by further depression of consciousness, increased systemic arterial blood pressure (SABP), bradycardia, and irregular respiration. In the fourth or terminal stage there is deep coma, a progressive fall in systemic arterial blood pressure and the pupils become fixed and dilated. The rise of intracranial pressure at this stage results in a fall in cerebral perfusion pressure (CPP) (CPP = SABP – ICP), with reduction in cerebral blood flow (CBF). The fall in cerebral perfusion pressure that accompanies a rise in intracranial pressure is recognized as being just as important as the rise in intracranial pressure itself.

This fall in cerebral perfusion pressure will be particularly dangerous if autoreguiation of cerebral blood flow is lost. For these reasons the management of cerebral perfusion pressure is now considered to be more important than the management of intracranial pressure alone. Evidence from randomized controlled trials shows that cerebral perfusion pressure should be maintained above 60 mm Hg if secondary insults to the brain are to be avoided.

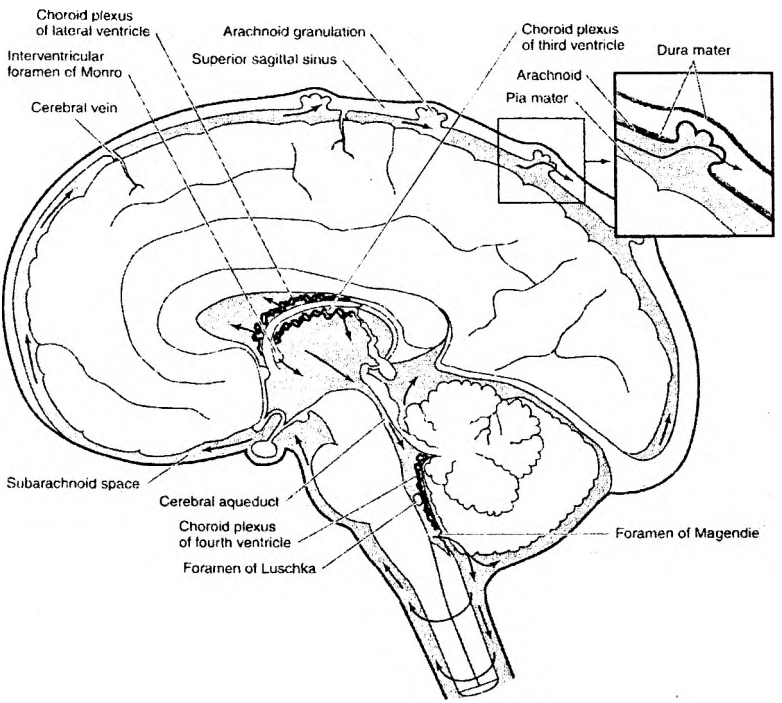


Fig. 12. Circulation of cerebrospinal fluid (CSF). CSF is produced by the choroid plexus, which consists of specialized secretory tissue located within the cerebral ventricles. It flows from the lateral and third ventricles through the cerebral aqueduct and fourth ventricle and exits the ventricular system through two laterally situated foramina of Luschka and a single, medially located foramen of Magendie. CSF then enters and circulates through the subarachnoid space surrounding the brain and spinal cord. It is ultimately absorbed through arachnoid granulations into the venous circulation. (From R. Simon, M. Aminoff, D. Greenberg, 1999)

The general effects of mass lesions

Initially, a slowly growing mass plays a relatively small part in raising intracranial pressure. Because of the partial division of the cranial cavity into compartments by the falx and tentorium, the local rise of pressure is partly confined to the cranial compartment; this is in contrast to the increased pressure throughout the craniospinal axis, which is usually produced by diffuse cerebral oedema, or to that which can be produced, for instance, following intracerebral haemorrhage (ICH) or subarachnoid haemorrhage (SAH). A rapid rise in intracranial pressure follows a simulated intracerebral haemorrhage. The rate of expansion of the mass determines the effectiveness of the compensatory mechanisms. A very slow-growing mass (e.g. a meningioma) reaches a large size without altering cerebral perfusion pressure or intracranial pressure, while a rapidly expanding mass (e.g. a haematoma) produces a large rise in intracranial pressure and a fall in cerebral perfusion pressure. Nevertheless, as compensation fails and the mass of the lesion increases, a volume/pressure curve can be derived, confirming the initial slight rise in intracranial pressure followed by an exponential increase, as it grows larger. As the intracranial pressure rises, cerebral perfusion pressure falls: maintenance of higher levels of cerebral perfusion pressure is associated with a better outcome in patients with head injury. The intracranial pressure waveform is a function of the arterial pressure waveform. Spectral analysis of these waves has shown six harmonic components; amplitude transfer functions can be clearly separated into four types, which reflect the degree of vascular compliance of the cerebral circulation. The recognition of the importance of cerebral perfusion pressure has made it possible to correlate marginally reduced cerebral perfusion in head-injured patients with transcranial Doppler and jugular venous oxygen measurements.

Brain herniation

Progressive expansion of the mass leads to herniation of brain tissue from the compartment in which the mass lesion lies. The principal herniation sites are: of the cinguiate gyrus beneath the falx cerebri (subfalcine herniation); of the medial temporal lobe through the tentorial hiatus (tentorial herniation); or of the cerebellar tonsils into the foramen magnum (the cerebellar pressure cone). In these circumstances, pressure gradients develop between the various intracranial compartments, depending upon that in which the mass lesion lies. The effects of these lesions will be considered later. Thus an early effect of a mass lesion is to displace CSF from the cranial cavity. Lumbar puncture carries grave risks in any tumour suspect, as the removal of fluid with resultant reduced pressure in the lumbar theca may induce herniation. Additionally, it must be noted that mass lesions, depending upon their situation, can also obstruct the outflow of CSF from one lateral ventricle (due to pressure occlusion of the foramen of Monro), from

the third ventricle (due to occlusion of the aqueduct), or from the fourth ventricle, giving rise to hydrocephalus with dilatation of one or more of the ventricles, thus causing an even greater increase in intracranial pressure.

Circulatory effects

The effect of intracranial pressure upon the cerebral circulation is also important. Compression of venous sinuses and cortical veins increases venous pressure, thus contributing to the rise in intracranial pressure. Also, it is one factor responsible for inducing cerebral oedema, an important complication of intracranial mass lesions, which is often most severe in the neighbourhood of the tumour. Thus, brain swelling may be due either to vascular mechanisms or to brain oedema. Compression of arteries may reduce blood flow focally or generally (if there is a fall in cerebral perfusion pressure) and infarction may result. A fall in cerebral perfusion pressure below 50 mmHg has been shown to reduce cerebral blood flow (CBF).

However, in head injury, subarachnoid haemorrhage, and intracerebral haemorrhage, normal autoregulation is lost and higher levels of cerebral perfusion pressure may be needed to maintain cerebral blood flow. Arterial hypertension may develop as a compensatory mechanism, the Cushing response, partially in attempted compensation for the increased cerebral arterial resistance and so as to increase cerebral perfusion pressure. There may also be electrocardiographic abnormalities such as prominent V-waves, ST-T segment changes, notched T-waves, and prolonged (or shortened) Q-T intervals. Any arrhythmia may develop, particularly if there is associated haemorrhage. The rise in systemic arterial blood pressure, and perhaps the electrocardiographic changes, are thought to result, at least in part, from medullary ischaemia due to stretching of perforating branches of the basilar artery, induced in turn by downward brainstem displacement. The situation may also be influenced by the cerebral vasodilatation induced by hypercapnia or hypoxia. These, in turn, may be a consequence of the respiratory irregularities induced by intracranial pressure. However, these factors, like volatile anaesthetic agents, also increase intracranial pressure. Conversely, hyperventilation and consequent hypocapnia reduce it, as do hypothermia, hyperbaric oxygen, and some drugs.

Skull rigidity

The effects of the rigidity of the skull must also be considered. That of the adult is rigid and unyielding. So, as the intracranial pressure rises, an important consequence visible radiologically is that chronic downward pressure, sometimes of a dilated third ventricle, upon the sella turcica may initially cause decalcification and later erosion of the posterior clinoid processes. Sometimes the sella enlarges, occasionally resulting in an empty sella syndrome, occasionally with clinical manifestations of hypopituitarism.

By contrast, non-union of the cranial sutures in infants provides a partial safety valve, so that increased intracranial pressure leads to increased head circumference. This often occurs in hydrocephalus. In children a rise in intracranial pressure may lead to separation of the cranial sutures. Premature union of the sutures (craniostenosis) causes a marked increase in intracranial pressure because skull growth is arrested while a normal brain is still increasing in size.

Symptoms

Symptoms of chronic elevation of intracranial pressure are headache, vomiting, papilloedema, and depression of consciousness. The headache associated with an increased intracranial pressure, especially when resulting from mass lesions, is mainly due to compression or distortion of the dura mater and of the pain-sensitive intracranial blood vessels. It is often paroxysmal, at first worse on waking or after recumbency, throbbing in character, corresponding with the arterial pressure wave. Exertion, coughing, sneezing, vomiting, straining, or sudden changes in posture accentuate it. Such headache is often frontal or occipital or both. Its distribution is of little localizing value, though it is occasionally unilateral, occurring upon the side of the mass lesion. Lesions in the posterior fossa often give suboccipital headache, and may give warning of the presence of a cerebellar pressure cone if there is associated neck stiffness or if pain is increased by attempted neck flexion. The vomiting that accompanies increased intracranial pressure often occurs in the mornings when the headache is at its height. It is generally attributed to compression or ischaemia of the vomiting centre in the medulla oblongata. Similarly, the bradycardia, which is also common, results from dysfunction in the cardiac centre but, in some patients with infra tentorial lesions, tachycardia eventually develops.

Papilloedema develops more rapidly with mass lesions in the posterior fossa because of their especial tendency to cause sudden obstructive hydrocephalus. In contrast, it often appears late in patients with prefrontal lesions. Obstruction of CSF flow in the subarachnoid space and impaired absorption both appear to be important factors in patients with tumours. Papilloedema is sometimes worse on one side, but it is rarely unilateral, except in the uncommon Foster Kennedy syndrome in which a subfrontal neoplasm on one side, often a meningioma, may compress the ipsilateral optic nerve, giving optic atrophy on that side and papilloedema on the other.

Breathing control is often impaired. Slow and deep respiratory movements often accompany a sudden rise in intracranial pressure sufficient to impair consciousness. Later, breathing may become irregular, Cheyne-Stokes respiration, and periods of apnoea then alternate with phases during which breathing waxes and wanes in amplitude. Central neurogenic hyperventilation, or so-called apneustic or ataxic breathing, are less common effects of brainstem compression or distortion but, in terminal coma, breathing is often rapid or shallow. These abnormalities of respiratory rate and rhythm may be due to compression or dis-

tortion of the brain stem. More often they result from median raphe haemorrhages or infarcts in the midbrain and pons, themselves resulting from tentorial herniation.

'False localizing signs' may also arise as a consequence of a sustained rise in intracranial pressure. These include unilateral or bilateral sixth-nerve palsies due to compression of the trunks of one or both nerves as they cross the apex of the petrous temporal bone, and bilateral extensor plantar responses or grasp reflexes resulting from ventricular dilatation in hydrocephalus, a third-nerve palsy. Less common false localizing signs include facial pain or sensory loss due to compression of the Gasserian ganglion in tentorial herniation; an ipsilateral extensor plantar response due to compression of the opposite cerebral peduncle against the free tentorial edge in tentorial herniation (Kernohan's sign); signs of cerebellar dysfunction rarely resulting from a massive frontal lesion and due to downward displacement of the brainstem; and bilateral, fixed, dilated pupils or defects of upward conjugate gaze due to a central cerebellar lesion displacing the midbrain upwards.

Cerebral herniations

Subfalcine herniations

Subfalcine herniations, that is herniation of the cingulate gyrus beneath the free edge of the falx cerebri, can be identified by angiography or magnetic resonance imaging (MRI). The ipsilateral lateral ventricle is often reduced in size. Usually there are no specific clinical features. Focal necrosis may affect the cingulate gyrus, or extensive frontal infarction may result from compression of the pericallosal arteries.

Tentorial herniation

Tentorial herniation most often develops as a consequence of lesions in the temporal lobe but may complicate any supratentorial mass lesion. As the herniated medial temporal lobe descends in the tentorial hiatus, the midbrain is pushed to the opposite side and downwards, and the opposite cerebral peduncle is compressed against the free edge of the contralateral tentorium. As a result, the aqueduct becomes compressed, and the ipsilateral third nerve is compressed against the tentorial edge, giving first a dilated, fixed pupil and later other signs of a third-nerve palsy. There may be grooving of the uncus and hippocampal gyrus with focal necrosis or infarction.

As herniation increases, there is further downward displacement of the brainstem. The principal complications of this process are: paresis or paralysis of upward conjugate gaze due to compression of the tectal plate; pressure upon one or both posterior cerebral arteries, giving unilateral or bilateral occipital-lobe infarction with consequent hemianopia or cortical blindness; and, most importantly, median raphe haemorrhages or infarction in the brainstem, due to ve-

nous obstruction or more often to shearing effects upon perforating branches of the basilar artery, so that irreversible coma results from necrosis of the reticular substance.

Tonsillar herniation

Tonsillar herniation, a cerebellar pressure cone through the foramen magnum, may complicate supratentorial, or particularly infratentorial, lesions. It produces haemorrhagic infarction of the cerebellar tonsils and also compression of the medulla with respiratory and/or cardiac arrest and death, when there is associated downward displacement of the brainstem.

Infratentorial lesions

Infratentorial lesions tend to cause obstructive hydrocephalus because of tonsillar herniation and the effects upon the brainstem, aqueduct, and fourth ventricle. Medullary or cerebellar infarction may occur due to compression of the medulla in the foramen magnum or compression of the posterior inferior cerebellar arteries. Sometimes reversed tentorial herniation occurs, with upward displacement of the brainstem and of the posterior fossa contents. This causes infarction of the superior aspects of the cerebellar hemispheres due to compression of the superior cerebellar arteries. Distortion of the hippocampal gyri due to upward pressure is rarely seen.

BENIGN INTRACRANIAL HYPERTENSION

This disorder was recognized in the pre-CT scan era as one in which there was high intracranial pressure with no mass lesion, initially called pseudotumour cerebri. It was sometimes known as 'otitic hydrocephalus' because of its association with chronic ear disease. The term 'benign intracranial hypertension' was used to describe a persistent rise of CSF pressure in the absence of a space-occupying lesion and with ventricles of normal or even reduced size. Usually it occurs in women, with a peak incidence in the third and fourth decades. They are often obese, and there is an association with oral contraceptive usage, pregnancy, and miscarriage. In a smaller group, affecting the sexes equally, there is a previous history of middle-ear disease, non-specific infection, or mild head injury. The condition may occur in children (1/100000 annually) and girls are three times more likely to be affected than boys. It has been suggested that benign intracranial hypertension is associated with brain swelling. possibly related to increased venous pressure from raised intraabdominal pressure. Many other pathogenetic associations have been postulated to explain this brain swelling, including hypervitaminosis A, the administration of a variety of antibiotics, an abnormality of the cerebral microvasculature with increased water content of the

brain, increased CSF production associated with an increase in circulating oestrogen, and increased CSF outflow resistance. The CT scan has shown that the ventricles are usually small. The brain swelling in benign intracranial hypertension is not associated with any MRI evidence of a structural abnormality, white matter oedema, or cerebral venous sinus thrombosis. The cerebrospinal fluid (CSF) is acellular and usually has a slightly low protein content. Other causes of raised intracranial pressure without an intracranial mass lesion or ventricular enlargement include venous thrombosis of the transverse or sigmoid sinus, chronic infective or neoplastic meningitis, or other causes of high protein in the CSF. These conditions can usually be distinguished by anatomic MRI or MR angiography and CSF analysis. Head injury with a depressed fracture over a venous sinus may also produce intracranial hypertension.

Headache is the most commonest complaint, and often having a vascular character or the classical headache of raised intracranial pressure. It is sometimes associated with postural obscuration of vision and occasional vomiting. There can be facial numbness or diplopia related to a sixth-nerve palsy. However, apart from tinnitus, other cranial nerve abnormalities are uncommon. By definition, papilloedema is expected, but there may be cases of headache with documented raised intracranial pressure without papilloedema. In the acute stage papilloedema may constitute a serious threat to vision, due either to associated peripapillary haemorrhages or to enlargement of the blind spot, which eventually may encroach on the macula. Blindness or permanent central scotomas occur. Usually the condition is benign if appropriately treated, with a good prognosis.

Imaging with CT or MRI shows no abnormality and MR angiography helps to exclude any sinus thrombosis that may require treatment with anticoagulants. Full blood count, and a hypercoagulable tendency should be checked. Frequent monitoring of the visual acuity and documentation of the visual fields is important to assess the response to treatment.

The mainstay of treatment in obese patients is weight reduction, and can be successful. Weight reduction after gastric surgery has been reported to be very successful in resistant cases, all showing resolution of cranial nerve dysfunction. Oral contraception should be stopped. However, if vision is threatened, emergency reduction of intracranial pressure is essential: this can be achieved simply by doing a lumbar puncture, a series of lumbar punctures, or by inserting a lumbar drain or lumbar-subcutaneous shunt. More permanent CSF diversion can be achieved with lumbarperitoneal or ventricular-peritoneal shunting, although the latter may be difficult because of the very small ventricles in some cases. Treatment of any underlying cause is important. Acetazolamide has also been used with some success. In severe benign intracranial hypertension, treatment with lumbar puncture and high doses of the steroid dexamethasone (4 mg four times a day) will rapidly reduce intracranial pressure, cerebral oedema, and the threat to vision. In occasional cases with severe papilloedema leading to rap-

idly failing vision, additional shunting procedures may be needed as an emergency measure. Surgical treatments include optic nerve sheath fenestration and subtemporal decompression. The more radical surgical interventions are for refractory cases with threatened vision when less invasive interventions have failed.

CEREBRAL OEDEMA

Knowledge about brain oedema has changed dramatically with recent developments in MRI. Cerebral oedema accompanies many brain pathologies and contributes to the resultant morbidity and mortality. It plays a major role in head injury, stroke, and brain tumour, brain abscess, encephalitis, meningitis, lead encephalopathy, hypertensive encephalopathy, hypoxia, hypo-osmolality, dialysis dysequilibrium, diabetic ketoacidosis, and obstructive hydrocephalus. Brain oedema can now be measured accurately *in vivo* with MRI. The distribution of water in neurons, glia, endothelial cells, and in the interstitial spaces can be determined with diffusion-weighted imaging (DWI). The oscillation of water molecules depends upon the space available within and between cells: when space is limited, movement of molecules is limited and this 'squeeze' can be measured with MRI and expressed as activated diffusion coefficients (ADC). So, if cells fill with water *(cytotoxic oedema),* they swell and reduce the interstitial space, thus reducing the activated diffusion coefficient. This ability to oscillate determines the diffusion of water molecules, so that diffusion-weighted imaging measures the interstitial water content. When the interstitial space becomes filled with water, for example around a brain tumour, the activated diffusion coefficient increases because water molecules are free to oscillate and diffuse over greater distances. This type of intercellular oedema is known as *vasogenic oedema* and is associated with an increased activated diffusion coefficient.

Brain oedema must be distinguished from engorgement due to an increase in the blood volume of the brain due to venous obstruction or vasodilatation. However, prolonged venous engorgement may lead to brain oedema. If localized or mildly generalized, oedema produces few symptoms and signs. If severe, it may cause major focal signs if it is localized to one cerebral hemisphere, and if generalized, it can give rise to the brain herniation described above.

Cerebral oedema was sub classified initially into vasogenic, cellular or cytotoxic, and interstitial (or hydrocephalic) types. A better understanding also comes from classifying brain oedema as open-barrier (vasogenic) and closed-barrier (cytotoxic) oedema.

Vasogenic (open-barrier) oedema

The vasogenic variety of oedema, associated with increased capillary permeability and an open blood-brain barrier (BBB), is the most common form

observed in clinical practice. It occurs in conditions such as tumour, abscess, haemorrhage, infarction, contusion, and purulent meningitis. The oedema is usually localized around the primary lesion. This produces focal symptoms and signs that are often more due to the oedema than to the primary lesion. It is associated with increased activated diffusion coefficients on diffusion-weighted imaging. Open-barrier oedema is much more likely to respond to intervention with steroids such as dexamethasone than the other types of cerebral oedema that are considered below.

Cytotoxic (closed-barrier) oedema

Cellular, or cytotoxic, oedema is characterized by swelling of all the cellular elements of the brain-neurons, glia, and endothelial cells-with an associated reduction in extracellular fluid but with an intact blood-brain barrier. It resembles that due to water intoxication in experimental animals, or that induced experimentally by triethyl tin, in which, however, there are also vacuoles and clefts in the cerebral white matter. It is characterized by swelling of all the cellular elements of the brain, with an associated reduction in extracellular fluid but with an intact blood-brain barrier. The activated diffusion coefficient on diffusion-weighted imaging is reduced. It occurs clinically in diffuse brain hypoxia, acute hypo-osmolality due to dilutional hyponatraemia, sodium depletion, or excess antidiuretic hormone (ADH) secretion, or in osmotic disequilibrium syndromes, such as in haemodialysis or diabetic ketoacidosis. The clinical manifestations are usually more generalized than in vasogenic oedema, and include drowsiness, stupor or coma, and sometimes convulsions. In ischaemic states a combination of vasogenic and cytotoxic oedema is often seen. The ultrastructural and molecular mechanisms occurring in the cell membrane are now becoming understood. Ischaemia results in the release of lactate and excitatory amino acids, glutamate and aspartate, which open receptor-activated calcium channels. In contrast, lactate does not rise very much or very early in traumatic oedema, which may therefore be different from ischaemic oedema. The influx of calcium leads to the activation of a-amino-hydroxyl-methyl proprionic acid (AMPA) and metabotropic receptors, with upregulation of genes, which may activate lysozymes, with resultant apoptosis. Massive increases in calcium lead to mitochondrial dysfunction, energy failure, cell membrane rupture, and necrosis. In Reye's syndrome, the oedema is cytotoxic and resembles that of triethyl tin intoxication.

Interstitial oedema

Interstitial or hydrocephalic oedema simply identifies the increased water content of the periventricular brain (largely extracellular), which is seen in hydrocephalus. The main site of accumulation of water is periventricular and manifests itself on CT scan as periventricular lucency.

Recognition of the type of oedema has implications with respect to treatment. High doses of steroids (dexamethasone, betamethasone) are of proven ef-

ficacy in most forms of vasogenic oedema but not in cytotoxic oedema. In cytotoxic oedema, osmotherapy with hypertonic mannitol or diuretics such as frusemide may be useful. While neuroprotective drugs appear to protect animals from the most severe effects of cerebral ischaemia, their role in the management of brain oedema is still uncertain. This applies particularly to the oedema seen with head injury, where prospective randomized controlled trials of steroids, barbiturates, N-methyl-D-aspartate (NMDA) receptor antagonists, and calcium antagonists have been shown not to improve outcome.

HYDROCEPHALUS

Hydrocephalus literally means water on the brain (Greek). As a definition, this is non-specific because atrophic dementia results in a passive increase in the volume of CSF in the head and such patients also have large ventricles but do not have hydrocephalus. Rather, hydrocephalus should be defined as an increase in the volume of the CSF within the skull due to an abnormality in its production, circulation, or absorption. This definition embraces those conditions in which there is at some stage an increased volume, and usually pressure, of CSF within the cranial cavity.

Aetiology

Hydrocephalus may be due to:

(1) increased formation of CSF;

(2) obstruction to the flow of fluid at some point between the choroid plexuses of the lateral ventricles from which it is secreted and the arachnoidal villi in the sagittal sinus through which it is reabsorbed; and

(3) impaired absorption of the fluid due to inflammation of the arachnoid (as in meningitis) or to thrombosis of the sagittal sinus.

Normal-pressure hydrocephalus is a clinical syndrome characterized by dementia, gait apraxia, and urinary incontinence.

Increased formation of CSF

Increased formation of CSF occurs with a choroid plexus papilloma. In such cases, removal of the tumour is usually curative, but occasionally hydrocephalus persists despite successful removal. Another rare syndrome of overproduction of CSF with deficient absorption is due to squamous metaplasia of the arachnoid villi but whether it occurs in humans remains undecided.

Obstruction

Obstruction to the CSF circulation may occur at any point of its course. Within the ventricles the most common cause is a neoplasm compressing one or both interventricular foramina or filling the third ventricle. The cerebral aqueduct may be obstructed by a tumour arising in the third ventricle, midbrain, or pineal body, or may be congenitally narrowed or even absent. Owing to its small calibre, slight swelling of its ependymal lining may lead to aqueduct obstruction, and cases have been reported in which hydrocephalus has been due to gliosis caused by ependymitis in this region. Aqueduct stenosis is a cause of infantile hydrocephalus but may give rise to increased intracranial pressure for the first time in adult life.

Posterior fossa tumours. Posterior fossa tumours may obstruct the fourth ventricle. Its foramina may be blocked by a congenital septum (the Dandy-Walker syndrome), by adhesions following meningitis, or by displacement of the medulla into the foramen magnum by the pressure of a tumour. The Dandy-Walker syndrome may be due to atresia of the foramina of Magendie and Luschka or to dysplasia of the cerebellum developing early in fetal life, as the cerebellar vermis is often absent or vestigial in such cases. The malformation may be accompanied by extra-axial leptomeningeal cysts in the posterior fossa, while such cysts alone may give a similar clinical and radiological picture. Within the subarachnoid space, obstruction may again be due to tumour, to traumatic adhesions, parasitic cysts, inflammation, haemorrhage, or to congenital abnormalities such as basilar impression or the Arnold-Chiari malformation.

The Arnold-Chiari malformation. The Arnold-Chiari malformation consists of congenital displacement of the cerebellar tonsils and of an elongated medulla oblongata downwards into the cervical canal. It prevents the egress of CSF from the fourth ventricle into the subarachnoid space. It is sometimes associated with lumbosacral spina bifida and with meningocele or meningomyelocele. When the caudal displacement of the cerebellar tonsils, fourth ventricle, and medulla into the cervical canal is associated with myelodysplasia, they may extend down to the mid-cervical region, and this anomaly is known as a Chiari type II. The Chiari type I anomaly is a simple ectasia of the cerebellar tonsils (down to C1) without any other primary malformation of the neuraxis. Congenital narrowing of the cerebral aqueduct sufficient to cause hydrocephalus was found in 10 of 20 such cases. MacFarlane and Maloney (1957) suggested that a Chiari malformation or, less often, the Dandy-Walker syndrome may result in dilatation of the central canal of the spinal cord early in life (hydromyelia) and that this is probably the most common mechanism causing syringomyelia.

The arachnoid villi

The arachnoid villi may be obstructed by inflammatory, neoplastic, or leukaemic cells in infective or neoplastic meningitis. Obstruction of the subarachnoid space and the arachnoid villi by blood accounts for the hydrocepha-

lus seen with subarachnoid haemorrhage and head injury. Absorption of fluid from the arachnoid villi may also be restricted by a rise in the intracranial venous pressure, by compression of venous sinuses by an intracranial tumour, or by impairment of venous drainage from the head due to raised intrathoracic pressure in cases of intrathoracic neoplasm or pulmonary hypertension. In general, venous obstruction results in brain swelling with a reduction in the size of the ventricles. Thrombosis of the superior sagittal sinus, caused by extension of inflammation from the transverse sinus, is one cause of the condition 'otitic hydrocephalus', in which symptoms of hydrocephalus complicate otitis media or mastoiditis.

Classification

Hypertensive hydrocephalus can be further subdivided into:

1. Obstructive hydrocephalus (once called internal hydrocephalus, and also known as non-communicating hydrocephalus), in which there is an obstruction to the circulation of the CSF, either within the ventricles or aqueduct, or at the outlet from the fourth ventricle. It prevents free communication between the ventricles and the subarachnoid space.

2. Communicating hydrocephalus (once called external hydrocephalus, and also known as non-obstructive hydrocephalus), in which hydrocephalus is due either to disturbance in the formation and absorption of CSF, or to an obstruction to its circulation in the subarachnoid space itself.

Congenital abnormalities are the most common cause of obstructive hydrocephalus in autopsy series, especially in neonates and perinatally. In 100 consecutive post-mortem examinations, malformation was the sole cause in only 14 per cent of cases, but in association with infection or trauma it accounted for 46 per cent. Inflammatory reaction due to infection or haemorrhage but without malformation accounted for another 50 per cent, the remaining 4 per cent being due to tumours.

In the past, a distinction was often made between 'congenital' and 'acquired' hydrocephalus, but this distinction is artificial. A congenital abnormality alone is the most likely cause of hydrocephalus developing before birth, but congenital and acquired factors often both contribute to hydrocephalus in infancy. Nor do congenital factors cease to operate later, since hydrocephalus developing in adult life may be the late result of aqueduct stenosis or Chiari malformation.

The more common causes of hydrocephalus developing in the absence of congenital abnormality are meningeal adhesions following meningitis or haemorrhage, arachnoiditis of obscure origin, thrombosis of intracranial venous sinuses, and intracranial tumour. Chronic inflammatory meningitis or arachnoiditis following tuberculosis are rare causes. Obstruction within the third or

fourth ventricle or in the subarachnoid space, may be due occasionally to parasitic cysts.

Pathophysiology

The rate of at which hydrocephalus develops determines the ventricular size. Acute obstructive hydrocephalus produces high intracranial pressure with only slight ventricular enlargement. Chronic obstruction may produce massive ventricles with only slightly elevated ICP. When obstruction occurs in the aqueduct, only the lateral and third ventricles are distended. When the obstruction is more caudal, the aqueduct and fourth ventricle may also be enlarged. Ventricular distension causes thinning of the cerebral hemispheres which, in severe cases, may be extreme, and is associated with marked atrophy of the white matter and loss of cortical ganglion cells. The ventricular ependyma is normal, except in inflammatory cases, when a localized or diffuse ependymitis may be present. Meningeal adhesions indicate previous meningitis. Distension of the ventricles leads to pressure upon the calvarium, which becomes thin, especially over the cerebral gyri. Separation of the sutures occurs when hydrocephalus develops in early life, but is not seen, as a rule, after adolescence. Compression of the base of the skull causes erosion of the clinoid processes and excavation of the sella turcica. The olfactory tracts and optic nerves are often atrophic.

Symptoms and signs

These are so dependent upon age and the deformability of the skull that it is useful to divide symptoms and signs into infantile and post-infantile. Nevertheless, infants with hydrocephalus may grow up with or without neurological and cognitive impairment, depending on the effectiveness and timeliness of treatment. The features of infantile hydrocephalus may therefore manifest in later life; leading to a degree of overlap when it comes to long-term disability.

Infantile hydrocephalus

Enlargement of the head is the most conspicuous sign in infantile hydrocephalus. It is being diagnosed with increased frequency before birth. The disorder becomes evident during the first few weeks of life owing to the large head, prominent scalp veins, and down-turning of the eyes, 'sun-setting sign'. It is slowly progressive. If untreated, the head may attain a huge size with a circumference of 75 cm or even more. The cranial sutures are widely separated and the anterior fontanelle is much enlarged. There is marked congestion of scalp veins. Enlargement of the head occurs in all diameters and in extreme cases it is translucent. The frontal region bulges forwards, and downward pressure upon the or-

bital plates causes the eyes to be protruded forwards and downwards. Fortunately such cases are rare today.

Owing to expansibility of the skull in infancy, symptoms of increased intracranial pressure are slight or absent. Hydrocephalic children seem little troubled by headache and rarely vomit. Convulsions are common. In neglected cases bilateral anosmia may occur. Optic atrophy due to pressure upon the nerves is usually present, but in rare cases there is papilloedema. Visual acuity may be progressively reduced until the child becomes blind. Paralysis of other cranial nerves may occur, and squint is not uncommon. Nystagmus may be present. In the limbs there are usually weakness and incoordination, generally more marked in the lower than in the upper limbs. Spasticity with exaggeration of tendon reflexes is common in the lower limbs, although sometimes tendon reflexes are lost. The plantar reflexes are usually extensor. There may be little or no disturbance of sensibility. The mental state varies. In severe cases there is usually reduced cognitive function and poor memory, but in milder cases this is slight or absent. Intelligence in later life may be surprisingly unimpaired in some cases, even when ventricular dilatation has progressed such that only 1 cm thickness of cerebral substance remains between the ventricles and the inner skull table. In milder cases there may be obesity and/or diabetes insipidus, due to compression of the hypothalamus and pituitary, and, in more severe cases, wasting. Cerebrospinal fluid rhinorrhoea is a rare complication. A unique hydrocephalic 'bobblehead doll syndrome' is characterized by two to four oscillations of the head per minute with psychomotor retardation and results from obstructive lesions in or near the third ventricle or aqueduct.

Hydrocephalus after infancy

The clinical picture of hydrocephalus developing after infancy varies according to its cause. In obstructive hydrocephalus, symptoms of increased intracranial pressure are conspicuous. Headache and vomiting are early symptoms and are often followed by the development of papilloedema. The headache is initially paroxysmal, but later becomes constant; there are sometimes intense exacerbations characterized by severe headache radiating down the neck associated with head retraction and even with opisthotonos, vomiting, and impairment of consciousness. Giddiness is a common symptom. Some mental deterioration usually occurs after a time, especially in later life. Hallucinations, delusions, and mood changes may occur. Convulsions are less common than in the infantile variety, and enlargement of the head does not occur after the age of 3 years, although slight separation of the sutures may occur until teenage years. In older children this slight separation of the cranial sutures yields a 'cracked-pot sound' on percussion and may be associated with venous congestion of the scalp. The skull remains of normal size following onset in adulthood, for instance in delayed presentation of cerebral aqueduct stenosis.Cranial-nerve palsies may oc-

cur, especially paresis of the sixth and seventh nerves, and symptomatic trigeminal neuralgia or facial sensory loss have been reported. Slight exophthalmos is not uncommon. Gross weakness of the limbs is absent, though clumsiness and slight incoordination are common. The tendon reflexes may be exaggerated or diminished. The plantar reflexes are often extensor. There is usually no sensory loss. Symptoms of hypopituitarism, obesity, and genital atrophy are common in children and adolescents.

Normal-pressure hydrocephalus

A form of late-onset communicating hydrocephalus is called 'low-pressure hydrocephalus' since, although the ventricles are dilated, the pressure within them at the time of measurement was either normal or only slightly raised. The clinical syndrome is characterized by the triad of progressive dementia, gait apraxia, and urinary incontinence. The CT scan has proved helpful but the findings are not invariably conclusive. Large ventricles and small sulci shown on the CT or MRI, however, are suggestive of this condition and continuous intracranial monitoring has shown significant B waves for at least 2 hours a day. This has been helpful in identifying patients who may benefit from surgery. Thus, while CSF pressure is usually normal or low, transient episodes of raised pressure occur in many cases. With MRI scanning it is possible to measure the volume of the ventricular CSF and to compare it with the volume of CSF in the subarachnoid spaces and fissures. In a large prospective study, the most reliable predictive feature of a good response to shunting was the absence of white matter changes on MRI scan. The most widely accepted test by neurologists and neurosurgeons is the CSF tap test, where there is clinical improvement following a lumbar puncture. Of all the tests available, the response to lumbar puncture is thought to be the most reliable. Serial psychometric tests are useful in assessing the response to treatment. These, together with a simple walking test, should be documented carefully before and after lumbar puncture.

The condition usually presents in middle or late life, sometimes with dementia alone or with the clinical picture of the parkinsonism-dementia complex and 'drop' attacks may occur. The cause of the communicating hydrocephalus is unexplained in most such cases, although it may follow subarachnoid haemorrhage or may develop many years after recovery from meningitis or head injury. Differential diagnosis from cerebral atrophy in dementia is clearly important, as shunting operations are of no value in the latter condition; however, no single method provides an absolutely reliable distinction.

Radiological diagnosis

Radiographs of the skull in hydrocephalus may show enlargement of the calvarium, with suture diastasis, thinning, and exaggeration of convolutional markings. However, this latter finding alone may be normal and is an unreliable guide to raised intracranial pressure. Separation of the sutures may be present in

children. The clinoid processes are often eroded and the sella turcica is deepened and expanded anteroposteriorly. CT and MR imaging give a clear picture of the ventricular size, and often the underlying cause is identified. MRI is superior to CT in identifying posterior fossa causes. The use of three-dimensional fast asymmetric spin-echo (FASE) MR imaging sequences strongly predicts a good response to shunting. Other MRI techniques to evaluate CSF flow have yielded conflicting results.

Monitoring/compliance

The most frequent form of monitoring is measurement of the head circumference in infants. This is routine in most hospitals and in primary care. Deviation from the percentile for a particular child should trigger referral for further assessment. Also, regular measurement of head circumference allows the efficacy (or otherwise) of treatment to be monitored over time.

Intracranial pressure monitoring may be useful when there is uncertainty about the need for CSF diversion. This may take place via the chamber of a shunt or reservoir inserted specifically for this purpose. In normal-pressure hydrocephalus, intracranial pressure monitoring may be helpful, particularly if pressure waveform analysis is undertaken. Non-invasive intracranial pressure monitoring is possible via the fontanelle in infants or with the tympanic membrane displacement test in adults.

Compliance (the reciprocal of elastance) may reflect the reserve capacity to withstand small changes in volume. It can now be measured directly with a continuous compliance monitor.

Prognosis

It has been recognized for many years that untreated infantile hydrocephalus is fatal during the first few years of life, on average a hydrocephalic alive at 3 months has a 26 per cent chance of reaching adult life without surgery, and survival to between 1 and 2 years is associated with a 50 per cent chance of reaching adulthood. Some who survive have mental retardation, epilepsy, or blindness. Even with underlying aqueduct stenosis, the hydrocephalic process often arrests spontaneously. In 41 per cent of 70 cases without spina bifida the IQ after 6 years was over 85, in 29 per cent below 50. The severity of hydrocephalus bears a close relationship to IQ and physical disability such as spasticity and ataxia. In the past many children with the Arnold-Chiari malformation and myelomeningocele died from infection of the sac or hydrocephalus.

The introduction of ventricular diversion procedures reduced the mortality of hydrocephalus with myelomeningocele to 30 per cent at the end of 2 years, and that of uncomplicated hydrocephalus to less than 20 per cent. Two-thirds of such cases treated surgically had an IQ of 75 or more. More recent figures have claimed IQs of more than 100 in 31 per cent and greater than 70 in 85 per cent. The prognosis of hydrocephalus after infancy depends upon its cause and how far this is amenable to treatment. In nontumorous hydrocephalus, IQs were greater than 90 in 32 per cent and greater than 70 in 60 per cent. Also, adults

who were treated for hydrocephalus due to spina bifida had poorer verbal and visuospatial memory performance than those with aqueduct stenosis.

Treatment by drainage

In an emergency, obstructive hydrocephalus can be treated by ventricular drainage through a burrhole or twistdrill. Drainage is usually maintained for up to 5 days via a closed system with a fixed-height drip-chamber. By contrast, communicating hydrocephalus can be treated by lumbar puncture or via a lumbar drain, provided that imaging has excluded any intracranial mass or tonsillar herniation. This is often the case with subarachnoid haemorrhage or meningitis. Because they can be set-up under local anaesthesia, such drainage methods may be used in emergency situations and in patients unfit for general anaesthesia. Permanent CSF diversion requires a general anaesthetic.

CSF diversion and shunts

In the past many operations, including excision of the choroid plexus, Torkildsen's ventriculo-cisternostomy, ventriculosubdural, ventriculo-ureteric, ventriculo-atrial and ventriculopleural drainage, were used, with varying degrees of success. Now there is general agreement that the treatment of choice is use of various shunts inserted into the lateral ventricle, with catheter drainage into the peritoneum. These shunts have differing hydrodynamic properties, which have been carefully evaluated. Most of them have low hydrodynamic resistance so that flow increases due to a siphoning effect when connected to a long distal catheter. Some shunts are programmable but they are all susceptible to siphoning. Colonization of the valves with Staphylococcus albus or diphtheroids may be asymptomatic for some time. The UK shunt registry has documented varying infection and revision rates in the 44 UK units. Revision rates ranged from 18 to 70 per cent and infection rates from 0 to 21 per cent.

The appropriate treatment of hydrocephalus after infancy depends upon its cause. A causative intracranial tumour must receive appropriate surgical treatment whenever possible. When there is a tumour in the third ventricle or midbrain or in some other area that is causing obstruction but cannot be removed or treated effectively by radiotherapy, temporary improvement may result from a shunting operation with insertion of a ventriculo-peritoneal (VP) shunt.

While early reports of ventriculo-peritoneal shunting in cases of low-pressure hydrocephalus were encouraging, with about two-thirds of all patients showing early intellectual as well as physical improvement, after 3 years less than half demonstrated continuing benefit. In yet another series of patients, only a third were improved, and 50 per cent of a similar group of patients not operated upon failed to deteriorate over a 3-year period; the surgical group also showed a high incidence of complications. Thus early optimism has not been borne out by good long-term results in all cases. In some longstanding cases,

there are irreversible neuropathological changes somewhat similar to those of Alzheimer's disease, although this is an inevitable occurrence in any large group of patients presenting with mild dementia. With good clinical diagnostic criteria and a positive CSF tap test, shunting undoubtedly leads to improvement in many patients.

Other treatments

Third ventriculostomy has been reintroduced with advances in endoscopic techniques. It is particularly useful when hydrocephalus is due to aqueduct stenosis. Lumbo-peritoneal shunting is as successful as VP shunting in communicating hydrocephalus, normal-pressure hydrocephalus, and benign intracranial hypertension, and has the advantage of not requiring ventricular cannulation through brain tissue.

Rare underlying causes need to be considered in all cases of hydrocephalus and may need prolonged treatment in their own right. Examples include antituberculous treatment for tuberculous meningitis or praziquantel for parasitic cysts.

SIGNS OF MENINGEAL IRRITATION

Neck stiffness

Ask the patient to flex the neck as fully as possible to ascertain the degree of movement possible, and then to relax. Then passively flex the neck. The chin should normally touch the chest without pain.

In meningeal irritation neck flexion causes pain in the posterior part of the neck, sometimes radiating down the back, and the movement is resisted by spasm in the extensor muscles of the neck. Neck rigidity is also caused by diseases of the cervical spine. Head retraction represents a marked degree of neck rigidity.

Kernig's sign

Kernig's sign is tested with the patient supine on the bed by passively extending the patient's knee when the hip is fully flexed. In patients with meningeal irritation affecting the lower part of the spinal subarachnoid space this movement causes pain and spasm of the hamstrings. It is a less sensitive test than neck stiffness.

These two tests depend upon the fact- that stretching the spinal nerve roots in meningeal irritation causes reflex muscular spasm in the paraspinal and sacral muscles. They are both positive in meningitis and subarachnoid haemorrhage, and also in patients with 'meningism', a state of irritation of the meninges seen most commonly in young children with acute fevers. In some patients with raised intracranial pressure in whom herniation of the cerebellar tonsils into the

foramen magnum has occurred, neck stiffness may also be present.

Straight leg raising

This test is useful in patients with sciatica. The sciatic nerve and its roots are stretched by passively elevating the patient's extended leg with the hand, which is placed behind the heel. The movement is restricted by sciatic pain when a lumbosacral spinal root is entrapped, as in lumbosacral intervertebral disc protrusion.

HEADACHE & FACIAL PAIN

Headache occurs in all age groups and is the seventh leading reason for medical office visits; the causes are myriad. Although most often a benign condition (especially when chronic and recurrent), headache of new onset may be the earliest or the principal manifestation of serious systemic or intracranial disease and therefore requires thorough and systematic evaluation.

An etiologic diagnosis of headache is based on understanding the pathophysiology of head pain; obtaining a history, with characterization of the pain as acute, subacute, or chronic; performing a careful physical examination; and formulating a differential diagnosis.

PATHOPHYSIOLOGY

Pain-Sensitive Structures

Headache is caused by traction, displacement, inflammation, vascular spasm, or distention of the painsensitive structures in the head or neck. Isolated involvement of the bony skull, most of the dura, or most regions of brain parenchyma does not produce pain.

A. Pain-Sensitive Structures Within the Cranial Vault. These include the venous sinuses (eg, sagittal sinus); the anterior and middle meningeal arteries; the dura at the base of the skull; the trigeminal (V), glossopharyngeal (IX), and vagus (X) nerves; the proximal portions of the internal carotid artery and its branches near the circle of Willis; the brain stem periaqueductal gray matter; and the sensory nuclei of the thalamus.

B. Extracranial Pain-Sensitive Structures. These include the periosteum of the skull; the skin; the subcutaneous tissues, muscles, and arteries; the neck muscles; the second and third cervical nerves; the eyes, ears, teeth, sinuses, and oropharynx; and the mucous membranes of the nasal cavity.

Radiation or Projection of Pain

The trigeminal (V) nerve carries sensation from intracranial structures in the anterior and middle fossae of the skull, above the cerebellar tentorium. Discrete intracranial lesions in these locations produce pain that radiates in the trigeminal nerve distribution.

The glossopharyngeal (IX) and vagus (X) nerves supply part of the posterior fossa; pain originating in this area may also be referred to the ear or throat (eg, glossopharyngeal neuralgia).

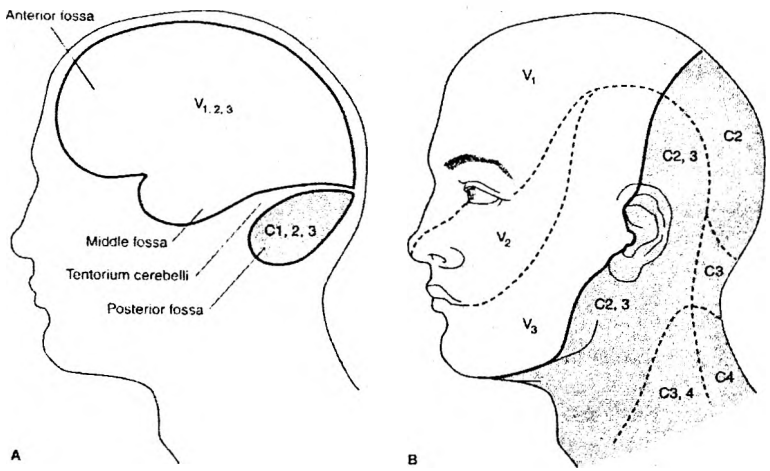


Fig. 13. Innervation of pain-sensitive intracranial compartments (A) and corresponding extracranial sites of pain radiation (B). The trigeminal (V) nerve, especially its ophthalmic (VI) division, innervates the anterior and middle cranial fossae; lesions in these areas can produce frontal headache. The upper cervical nerve roots (especially C2) innervate the posterior fossa; lesions here can cause occipital headache. (From R. Simon, M. Aminoff, D. Greenberg, 1999)

The upper cervical nerves transmit stimuli arising from infratentorial and cervical structures; therefore, pain from posterior fossa lesions projects to the second and third cervical dermatomes.

CAUSES OF HEADACHE AND FACIAL PAIN

Acute onset

Common causes

- Subarachnoid hemorrhage
- Other cerebrovascular diseases
- Meningitis or encephalitis
- Ocular disorders (glaucoma, acute iritis)

Less common causes

- Seizures
- Lumbar puncture
- Hypertensive encephalopathy
- Coitus

Subacute onset

- Giant cell (temporal) arteritis
- Intracranial mass (tumor, subdural hematoma, abscess)
- Pseudotumor cerebri (benign intracranial hypertension)
- Trigeminal neuralgia (tic douloureux)
- Glossopharyngeal neuralgia
- Postherpetic neuralgia
- Hypertension (including pheochromocytoma and the use of monoamine oxidase inhibitors plus tyramine)
- Atypical facial pain

Chronic

- Migraine
- Cluster headache
- Tension headache
- Cervical spine disease
- Sinusitis
- Dental disease

HISTORY

Classification & Approach to the Differential Diagnosis

A. Acute Headaches and Facial Pain. Headaches that are new in onset and clearly different from any the patient has experienced previously are commonly a symptom of serious illness and therefore demand prompt evaluation.

The sudden onset of "the worst headache I've ever had in my life" (classic subarachnoid hemorrhage), diffuse headache with neck stiffness and fever (meningitis), and head pain centered about one eye (acute glaucoma) are striking examples. Acute headaches may also accompany more benign processes such as viral syndromes or other febrile illnesses.

B. Subacute Headaches and Facial Pain. Subacute headaches occur over a period of weeks to months. Such headaches may also signify serious medical disorders, especially when the pain is progressive or when it develops in elderly patients. Inquiries should be made about recent head trauma (subdural hematoma or postconcussive syndrome); a history of malaise, fever, or neck stiffness (subacute meningitis); other neurologic abnormalities or weight loss (primary or metastatic brain tumor); symptoms of vasculitis, especially giant cell arteritis; and medical conditions (eg, optic neuritis in multiple sclerosis; cutaneous herpes zoster) or medications.

C. Chronic Headaches and Facial Pain. Headaches that have occurred for years (eg, migraine or tension headaches) usually have a benign cause, although each acute attack may be profoundly disabling. When treating these patients, it is important to determine whether the present headache is similar to those suffered previously or is new – and thus represents a different process.

Precipitating Factors

Precipitating factors can provide a guide to the cause of headache. Such factors include recent eye or dental surgery; acute exacerbation of chronic sinusitis or hay fever; systemic viral infection; tension, emotional stress, or fatigue; menses; hunger; ice cream; foods containing nitrite (hot dogs, salami, ham, and most sausage), phenylethylamine (chocolate), or tyramine (cheddar cheese); and bright lights. Precipitation of headache by alcohol is especially typical of cluster headache. Chewing and eating commonly trigger glossopharyngeal neuralgia, tic douloureux, and the jaw claudication of giant cell arteritis; these activities also trigger pain in patients with temporomandibular joint dysfunction. The use of oral contraceptive agents or other drugs such as nitrates may precipitate or exacerbate migraine and even lead to stroke. Intense headache can occur in response to coughing in patients with structural lesions in the posterior fossa; in other instances no specific cause for cough headache can be identified.

Prodromal Symptoms

Prodromal symptoms or auras, such as scintillating scotomas or other visual changes, often occur with migraine; they may also occur in patients with a seizure disorder who present with postictal headaches.

Characteristics of Pain

Headache or facial pain is most often described as throbbing; a dull,

steady ache; or a jabbing, lancinating pain. Pulsating, throbbing pain is frequently ascribed to migraine, but it is equally common in patients with tension headache. A steady sensation of tightness or pressure is also commonly seen with tension headache. The pain produced by intracranial mass lesions is typically dull and steady. Sharp, lancinating pain suggests a neuritic cause such as trigeminal neuralgia. Ice picklike pain may be described by patients with migraine, cluster headache, or giant cell arteritis.

Headache of virtually any description can occur in patients with migraine or brain tumors, however, so the character of the pain alone does not provide a reliable etiologic guide.

Location of Pain

Unilateral headache is an invariable feature of cluster headache and occurs in the majority of migraine attacks; most patients with tension headache report bilateral pain.

Ocular or retroocular pain suggests a primary ophthalmologic disorder such as acute iritis or glaucoma, optic (II) nerve disease (eg, optic neuritis), or retroorbital inflammation (eg, Tolosa-Hunt syndrome). It is also common in migraine or cluster headache.

Paranasal pain localized to one or several of the sinuses, often associated with tenderness in the overlying periosteum and skin, occurs with acute infection or outlet obstruction of these structures.

Headache from intracranial mass lesions may be focal ("it hurts right here"), but even in such cases it is replaced by bioccipital and bifrontal pain when the intracranial pressure becomes elevated.

Bandlike or occipital discomfort is commonly associated with tension headaches. Occipital localization can also occur with meningeal irritation from infection or hemorrhage and with disorders of the joints, muscles, or ligaments of the upper cervical spine.

Pain within the first division of the trigeminal nerve, characteristically described as burning in quality, is a common feature of postherpetic neuralgia.

Lancinating pain localized to the second or third division of the trigeminal nerve suggests tic douloureux.

The pharynx and external auditory meatus are the most frequent sites of pain caused by glossopharyngeal neuralgia.

Associated Symptoms

Manifestations of underlying systemic disease can aid in the etiologic diagnosis of headache and should always be sought.

Recent weight loss may accompany cancer, giant cell arteritis, or depression.

Fever or chills may indicate systemic infection or meningitis.

Dyspnea or other symptoms of heart disease raise the possibility of subacute infective endocarditis and resultant brain abscess.

Visual disturbances suggest an ocular disorder (eg, glaucoma), migraine, or an intracranial process involving the optic nerve or tract or the central visual pathways.

Nausea and vomiting are common in migraine and posttraumatic headache syndromes and can be seen in the course of mass lesions. Some patients with migraine also report that diarrhea accompanies the attacks.

Photophobia may be prominent in migraine and acute meningitis or subarachnoid hemorrhage.

Myalgias often accompany tension headaches, viral syndromes, and giant cell arteritis.

Ipsilateral rhinorrhea and lacrimation during attacks typify cluster headache.

Transient loss of consciousness may be a concomitant of both migraine and glossopharyngeal neuralgia.

Other Features of Headache

A. Temporal Pattern of Headache. Headaches from mass lesions are commonly maximal on awakening, as are sinus headaches. Headaches from mass lesions, however, increase in severity over time. Cluster headaches frequently awaken patients from sleep; they often recur at the same time each day or night. Tension headaches can develop whenever stressful situations occur and are often maximal at the end of a workday. Migraine headaches are episodic and may be worse during menses.

B. Conditions Relieving Headache. Migraine headaches are frequently relieved by darkness, sleep, vomiting, or pressing on the ipsilateral temporal artery, and their frequency is often diminished during pregnancy. Postlumbar-puncture headaches are typically relieved by recumbency, while headaches caused by intracranial mass lesions may be less severe with the patient standing.

C. Conditions Exacerbating Headache. Discomfort exacerbated by rapid changes in head position or by events that transiently raise intracranial pressure, such as coughing and sneezing, is often associated with an intracranial mass but can also occur in migraine. Anger, excitement, or irritation can precipitate or worsen both migraine and tension headaches. Stooping, bending forward, sneezing, or blowing the nose characteristically worsens the pain of sinusitis. Postural headache (maximal when upright, nearly absent when lying down) occurs with low CSF pressure caused by lumbar puncture, head injury, or spinal fluid leak.

Fluctuations in intensity and duration of the headache with no obvious cause, especially when associated with similar fluctuations in mental status, are seen with subdural hematoma.

D. History of Headache. The characteristics of the present headache should be compared with those of previous occurrences, since headache with features different from those previously experienced calls for careful investigation.

EXAMINATION

A general physical examination is mandatory, since headache is a nonspecific accompaniment of many systemic disorders. If possible, the patient should be observed during an episode of headache or facial pain.

Vital Signs

A. Temperature. Although fever suggests a viral syndrome, meningitis, encephalitis, or brain abscess, headache from these causes can occur without fever. Moreover, headache can accompany any systemic infectious illness.

B. Pulse. Tachycardia can occur in a tense, anxious patient with a tension headache or accompany any severe pain. Paroxysmal headache associated with tachycardia and perspiration is characteristic of pheochromocytoma.

C. Blood Pressure. Hypertension per se rarely causes headache unless the blood pressure elevation is acute, as with pheochromocytoma, or very high, as with early hypertensive encephalopathy. Chronic hypertension, however, is the major risk factor for stroke, which can be associated with acute headache. Subarachnoid hemorrhage is commonly followed by marked acute blood pressure elevation.

D. Respiration. Hypercapnia from respiratory insufficiency from any cause can elevate intracranial pressure and produce headache.

General Physical Examination

A. Weight Loss. Weight loss or cachexia in a patient with headache suggests the presence of cancer or chronic infection. Polymyalgia rheumatica-giant cell arteritis syndromes can also be accompanied by weight loss.

B. Skin. Focal cellulitis of the face or overlying the skull indicates local infection, which may be the source of intracranial abscess or venous sinus thrombosis. Cutaneous abnormalities elsewhere may suggest vasculitis (including that from meningococcemia), endocarditis, or cancer. The neurofibromas or cafe-au-lait spots of von Recklinghausen's disease (neurofibromatosis) may be associated with benign or malignant intracranial tumors that produce headache. Cutaneous angiomas sometimes accompany arteriovenous malformations (A VMs) of the central nervous system and may be associated with chronic headache – or acute headache if they bleed. Herpes zoster that affects the face and head most often involves the eye and the skin around the periorbital tissue, causing facial pain.

C. Scalp, Face, and Head. Scalp tenderness is characteristic of migraine headache, subdural hematoma, giant cell arteritis, and postherpetic neuralgia. Nodularity, erythema, or tenderness over the temporal artery suggests giant cell arteritis. Localized tenderness of the superficial temporal artery also accompanies acute migraine. Recent head trauma or a mass lesion can cause a localized area of tenderness.

Paget's disease, myeloma, or metastatic cancer of the skull may produce head pain that is boring in quality and associated with skull tenderness. In Paget's disease, arteriovenous shunting within bone may make the scalp feel warm.

Disorders of the eyes, ears, or teeth may cause headache. Tooth percussion may reveal periodontal abscess. Sinus tenderness may indicate sinusitis. A bruit over the orbit or skull suggests an intracranial AVM, a carotid artery-cavernous sinus fistula, an aneurysm, or a meningioma. Lacerations of the tongue raise the possibility of postictal headache. Ipsilateral conjunctival injection, lacrimation, Horner's syndrome, and rhinorrhea occur with cluster headache. Temporomandibular joint disease is accompanied by local tenderness and crepitus.

D. Neck. Cervical muscle spasms occur with tension and migraine headaches, cervical spine injuries, cervical arthritis, or meningitis. Carotid bruits may be associated with cerebrovascular disease.

Meningeal signs must be carefully sought, especially if the headache is of recent onset. Meningeal irritation causes nuchal rigidity mainly in the anteroposterior direction, while cervical spine disorders restrict movement in all directions. Discomfort or hip and knee flexion during neck flexion (Brudzinski's sign) readily indicates meningeal irritation.

Meningeal signs may be absent or difficult to demonstrate in the early stages of subacute (eg, tuberculous) meningitis, in the first few hours after subarachnoid hemorrhage, and in comatose patients.

E. Heart and Lung. Brain abscess may be associated with congenital heart disease, which is evidenced by murmurs or cyanosis. Lung abscess may also be a source of brain abscess.

NEUROLOGIC EXAMINATION

Mental Status Examination

During the mental status examination, patients with acute headache may demonstrate confusion, as is commonly seen with subarachnoid hemorrhage and meningitis. Dementia may be the major feature of intracranial tumor, particularly one in the frontal lobe.

Cranial Nerve Examination

Cranial nerve abnormalities may suggest and localize an intracranial tu-

mor or other mass lesion. Papilledema, the hallmark of increased intracranial pressure, may be seen in space-occupying intracranial lesions, carotid artery-cavernous sinus fistula, pseudotumor cerebri, or hypertensive encephalopathy. Superficial retinal (subhyaloid) hemorrhages are characteristic of subarachnoid hemorrhage in adults. Ischemic retinopathy may be found in patients with vasculitis.

Progressive oculomotor nerve palsy, especially when it causes pupillary dilatation, may be the presenting sign of an expanding posterior-communicating-artery aneurysm, or it may reflect increasing intracranial pressure and incipient herniation. Decreased pupillary reactivity occurs in optic neuritis. Extraocular muscle palsies occur in Tolosa-Hunt syndrome. Proptosis suggests an orbital mass lesion or carotid artery-cavernous sinus fistula.

Decreased sensation over the area of pain-most commonly the first division of the trigeminal nerveis found in postherpetic neuralgia. Trigger areas eliciting pain in and about the face and pharynx suggest trigeminal and glossopharyngeal neuralgia, respectively.

Motor Examination

Asymmetric motor function or gait ataxia in a patient with a history of subacute headache demands complete evaluation to exclude intracranial mass lesions.

Sensory Examination

Focal or segmental sensory impairment or diminished corneal sensation (corneal reflex) is strong evidence against a benign cause of pain.

ACUTE HEADACHES

Sudden onset of new headache may be a symptom of serious intracranial or systemic disease; it must be investigated promptly and thoroughly.

CEREBROVASCULAR DISORDERS

The classic presentation of subarachnoid hemorrhage is the sudden onset of an unusually severe generalized headache. The absence of headache essentially precludes the diagnosis. Loss of consciousness is frequent, as are vomiting and neck stiffness. Symptoms may begin at any time of day and during either rest or exertion. The most significant feature of the headache is that it is new. Milder but otherwise similar headaches may have occurred in the weeks prior to the acute event. These earlier headaches are probably the result of small prodromal hemorrhages (sentinel, or warning, hemorrhages) or aneurysmal stretch. The headache is not always severe, however, especially if the subarachnoid hemorrhage is from a ruptured AVM rather than an aneurysm. Although the du-

ration of the hemorrhage is brief, the intensity of the headache may remain unchanged for several days and subside only slowly over the next 2 weeks. A recrudescent headache usually signifies recurrent bleeding.

Headache may be associated with – or may rarely be the presenting symptom of – thrombotic or embolic stroke. Compression of pain-sensitive structures is the mechanism of headache in intracranial hemorrhage, while pain-sensitive receptors in large cerebral arteries are responsible for headache in thrombotic and embolic stroke. Lacunar strokes, which affect small arterial branches deep in the brain, are not as frequently associated with headache.

Headaches associated with ischemic stroke are typically mild to moderate in intensity, ipsilateral to the involved hemisphere, and nonthrobbing in character. Their location is determined by the pain projection sites of the involved arteries: posterior fossa strokes usually present with occipital headache, whereas carotid lesions usually produce frontal (trigeminal distribution) pain. Transient ischemic attacks may be associated with headache in as many as 50% of cases; in perhaps one-third of these, headaches precede the other symptoms.

Headache accompanying retinal artery embolism or posterior cerebral artery spasm or occlusion may be erroneously diagnosed as migraine because of the associated visual impairment.

Headache also occurs following carotid endarterectomy and may be associated with focal sensory or motor signs of contralateral hemispheric ischemia. This syndrome occurs in the presence of a patent carotid artery on the second or third postoperative day and typically produces intense throbbing anterior headache that is often associated with nausea.

Headache disorders associated with ischemic or hemorrhagic cerebral infarction require direct treatment of the cerebral lesion combined with the use of analgesics for symptomatic relief.

MENINGITIS OR ENCEPHALITIS

Headache is a prominent feature of inflammation of the brain (encephalitis) or its meningeal coverings (meningitis) caused by bacterial, viral, or other infections; granulomatous processes; neoplasms; or chemical irritants. The pain is caused by inflammation of intracranial pain-sensitive structures, including blood vessels at the base of the brain. The headache syndrome produced is commonly throbbing in character, bilateral, and occipital or nuchal in location. The headache is increased by sitting upright, moving the head, compressing the jugular vein, or performing other maneuvers (eg, sneezing, coughing) that transiently increase intracranial pressure. Photophobia may be prominent. The headache rarely presents suddenly but more commonly develops over hours to days, especially with subacute infections (eg, tuberculous meningitis).

Neck stiffness and other signs of meningeal irritation must be sought with care, since they may not be obvious either early in the course of the illness or when the brain parenchyma, rather than meninges, is the predominant site of involvement. Lethargy or confusion may also be a prominent feature.

The diagnosis is suggested by a CSF examination that shows an increased white blood cell count. Bacterial, syphilitic, tuberculous, viral, fungal, and parasitic infections may be distinguished by CSF VDRL, Gram's stain, acid-fast stain, India ink preparation and cryptococcal antibody assays, and cultures.

HYPERTENSIVE ENCEPHALOPATHY

Headache may be due to a sudden elevation in blood pressure such as is caused by pheochromocytoma, sexual intercourse, the combination of monoamine oxidase inhibitors and tyramine-containing foods such as cheddar cheese, or-the most important cause-malignant hypertension. Blood pressures of 250/150 mm Hg or higher – characteristic of malignant hypertension – produce cerebral edema and displace pain-sensitive structures. The pain is described as severe and throbbing. Other signs of diffuse or focal central nervous system dysfunction are present, such as lethargy, hemiparesis, or focal seizures on CT or MRI images, posterior white matter changes may be seen. Treatment is with antihypertensive drugs, but care must be taken to avoid hypotension, which can result in cerebral ischemia and stroke.

SEIZURES

Postictal headache that follows generalized tonicclonic seizures is frequently accompanied by resolving lethargy, diffuse muscle soreness, or tongue laceration. Although this headache requires no specific treatment, it is important to differentiate it from subarachnoid hemorrhage and meningitis. If doubt exists, lumbar puncture should be undertaken.

LUMBAR PUNCTURE

Postlumbar-puncture headache is diagnosed by a history of lumbar puncture – and by the characteristic marked increase in pain in the upright position and relief with recumbency. The pain is typically occipital, comes on 24-48 hours after the procedure (although it may be later), and lasts 1-2 days, but may be prolonged. Headache is caused by persistent spinal subarachnoid leak with resultant traction on pain-sensitive structures at the base of the brain. The risk of this complication can be reduced by using a small-gauge needle (22 gauge or

smaller) for the puncture and removing only as much fluid as needed for the studies to be performed. Lying flat afterward, for any length of time, does not lessen the incidence. Low-pressure headache syndromes are usually selflimited. When this is not the case, they may respond to the administration of caffeine sodium benzoate, 500 mg intravenously, which can be repeated after 45 minutes if headache persists or recurs upon standing. In persistent cases, the subarachnoid rent can be sealed by injection of autologous blood into the epidural space at the site of the puncture; this requires an experienced anesthesiologist. Headache similar in character to that caused by lumbar puncture occasionally occurs spontaneously. TI-weighted, gadolinium-enhanced MRI may show smooth enhancement of the pachymeninges, which may be confused with leptomeningeal enhancement.

OCULAR DISORDERS

Pain about the eye may occur in migraine and cluster headache and is also the presenting feature of iritis and glaucoma. **Acute iritis** produces extreme eye pain that is associated with photophobia. The diagnosis is confirmed by slit lamp examination; acute management involves pharmacologic dilatation of the pupil. **Angle-closure glaucoma** produces pain within the globe that radiates to the forehead. When it occurs after middle age, such a pain syndrome should prompt diagnostic tonometry. Acute treatment is with glycerol, 1 mL/kg orally, followed by pilocarpine, 2%, 2 drops every 15 minutes.

HEADACHES OF SUBACUTE ONSET

GIANT CELL ARTERITIS

This disorder, also known as temporal arteritis, is characterized by a subacute granulomatous inflammation (consisting of lymphocytes, neutrophils, and giant cells) that affects the external carotid arterial system, particularly the superficial temporal artery, and the vertebral artery. Inflammation of the pain-sensitive arterial wall produces the headache. Thrombosis may occur in the most severely affected arteries.

This syndrome, which affects women twice as frequently as men, is uncommon before age 50 and is frequently associated with nonspecific signs and symptoms, such as malaise, myalgia, weight loss, arthralgia, and fever (the polymyalgia rheumatic a complex). The headache can be unilateral or bilateral, fairly severe, and boring in quality. It is characteristically localized to the scalp,

especially over the temporal arteries. Scalp tenderness may be especially apparent when lying with the head on a pillow or brushing the hair. Pain or stiffness in the jaw during chewing Gaw claudication) is highly suggestive of giant cell arteritis and is due to arterial ischemia in the muscles of mastication. Involvement of the ophthalmic artery leads to permanent blindness in 50% of untreated patients; in half of these, blindness will become bilateral. The visual loss is most often sudden in onset. Although episodes of transient prodromal blindness have been reported, blindness is unusual as an initial symptom; however, it often occurs within the first month.

The diagnosis is made by biopsy of affected temporal arteries, which are characteristically thickened and nonpulsatile as well as dilated and tender. The temporal arteries may be affected in a patchy manner, and serial sections may be necessary to demonstrate histologic vasculitis. The erythrocyte sedimentation rate (ESR) is almost invariably elevated. The mean Westergren ESR is about 100 mm/h in giant cell arteritis (range, 29-144 mm/h) and in polymyalgia rheumatica (range, 58-160 mm/h). The normal upper limit of the Westergren ESR in elderly patients is reported to be only as high as 40 mm/h.

Consideration of this diagnosis demands prompt inpatient evaluation if vision is to be preserved. Therapy for giant cell arteritis is prednisone, 40-60 mg/d orally, with decreasing dosage usually after about 3 months, depending upon the clinical response. The sedimentation rate returns rapidly toward normal with prednisone therapy and must be maintained within normal limits as the drug dose is tapered. Therapy should not be withheld pending biopsy diagnosis and should be continued despite negative biopsy findings if the diagnosis can be made with confidence on clinical grounds. Therapy generally has to be continued for 1-2 years. Although dramatic improvement in headache occurs within 2-3 days after institution of therapy, the blindness is usually irreversible.

INTRACRANIAL MASS

The new onset of headache in middle or later life should always raise concern about a mass lesion. A mass lesion, such as a brain tumor, subdural hematoma, or abscess, may or may not produce headache depending upon whether or not it compresses or distorts pain-sensitive intracranial structures. Only 30% of patients with intracranial tumor present with headache as the first symptom, although 80% have such a complaint at the time of diagnosis. Subdural hematoma frequently presents with conspicuous headache, since its large size increases the likelihood of impinging upon pain-sensitive areas. Headaches associated with brain tumors are most often nonspecific in character, mild to moderate in severity, dull and steady in nature, and intermittent. The pain is characteristically bifrontal, worse ipsilaterally, and aggravated by a change in position or by maneuvers that increase intracranial pressure, such as coughing, sneezing, and strain-

ing at stool. The headache is classically maximal on awakening in the morning and is associated with nausea and vomiting.

An uncommon type of headache that suggests brain tumor is characterized by a sudden onset of severe pain reaching maximal intensity within seconds, persisting for minutes to hours, and subsiding rapidly. Altered consciousness or "drop attacks" may be associated. Although classically associated with third ventricular colloid cysts, these paroxysmal headaches can be associated with tumors at many different intracranial sites.

Suspicion of an intracranial mass lesion demands prompt evaluation, preferably with CT scan or MRI. Lumbar puncture should not be used as a diagnostic screening test, since the results are nonspecific and the procedure may aggravate the symptoms of the intracerebral mass, sometimes with a fatal outcome.

PSEUDOTUMOR CEREBRI

Pseudotumor cerebri (benign intracranial hypertension) is characterized by a diffuse increase in intracranial pressure causing headache, papilledema, and diminished visual acuity. Diplopia may also occur as a result of abducens nerve palsy. Although pseudotumor can accompany many disorders, most cases are idiopathic. In the idiopathic variety, women are affected much more commonly than men, with a peak incidence in the third decade. Diffuse headache is almost always a presenting symptom, and diplopia and blurred vision occur in 60% of cases. Although visual acuity is normal in 50% of patients at presentation, moderate to severe papilledema is seen in almost 90%. Visual loss from increased intracranial pressure can occur even in the idiopathic form; episodes of clouded vision precede the loss.

The course of the idiopathic disorder is generally self-limited over several months, with no sequelae if intracranial pressure is maintained at a relatively normal level to prevent secondary optic atrophy. Differentiating idiopathic pseudotumor cerebri from intracerebral mass lesions and from some other disorders is critical; evaluation must include MRI or CT brain scanning. These studies typically show small (slitlike) ventricles in pseudotumor cerebri. Elevation of intracranial pressure can be documented by lumbar puncture. If a specific cause is identified, it must be treated appropriately.

Treatment with acetazolamide, 250 mg orally three times daily, with or without a diuretic (eg, furosemide), may be adequate to control mild intracranial hypertension. In other instances, prednisone, 60-80 mg/d orally, may be necessary. In refractory cases, repeated lumbar punctures or lumboperitoneal shunting procedures protect vision and decrease headache. Transorbital optic nerve sheath fenestration is also used to protect the optic nerve from the pressure injury that is thought to cause blindness.

TRIGEMINAL NEURALGIA

Trigeminal neuralgia (tic douloureux) is a facialpain syndrome of unknown cause that develops in middle to late life. In many instances, the trigeminal nerve roots are close to some vascular structure, and microvascular compression of the nerve is believed to cause the disorder. Pain is confined mainly to the area supplied by the second and third divisions of the trigeminal nerve. Involvement of the first division or bilateral disease occurs in less than 5% of cases. Characteristically, lightninglike momentary jabs of excruciating pain occur and spontaneously abate. Occurrence during sleep is rare. Painfree intervals may last for minutes to weeks, but long-term spontaneous remission is rare. Sensorystimulation of trigger zones about the cheek, nose, or mouth by touch, cold, wind, talking, or chewing can precipitate the pain. Physical examination discloses no abnormalities. Rarely, similar pain may occur in multiple sclerosis or brain stem tumors, and these possibilities should thus be considered in young patients and in all patients who show neurologic abnormalities on examination.

In idiopathic cases, CT scan and MRI fail to show any abnormality, and arteriography is similarly normal. Any vascular structure compressing the nerve roots is generally too small to be seen by these means.

Remission of symptoms with carbamazepine, 400-1200 mg/d orally in three divided doses, occurs within 24 hours in such a high percentage of cases that some believe it to be diagnostic. Rarely, blood dyscrasia occurs as an adverse reaction to carbamazepine. Intravenous administration of phenytoin, 250 mg, will abort an acute attack, and phenytoin, 200-400 mg/d orally, may be effective in combination with carbamazepine if a second drug is necessary. Lamotrigine 400 mg/d or baclofen 10 mg three times daily-20 mg four times daily has been used in refractory cases. Posterior fossa microvascular decompressive surgery has been used in drug-resistant cases.

GLOSSOPHARYNGEAL NEURALGIA

Patients with glossopharyngeal neuralgia, an uncommon pain syndrome, present with either a paroxysmal pain that is identical in quality to that of trigeminal neuralgia, or a continuous burning or aching discomfort. The pain is localized to the oropharynx, the tonsillar pillars, the base of the tongue, or the auditory meatus. The trigger areas are usually around the tonsillar pillars, so that symptoms are initiated by swallowing or by talking. Paroxysms of pain can occur many times daily and may be accompanied by syncopal episodes caused by transient bradyarrhythmias. Men are affected more often than women, and symptoms begin at a somewhat younger age than in trigeminal neuralgia. The diagnosis is established by the history and by reproducing pain through stimula-

tion of the trigger zones. Examination reveals no abnormal neurologic signs. Application of local anesthetics to the trigger area may block the pain response. Carbamazepine or phenytoin therapy (as described above for trigeminal neuralgia) usually produces dramatic relief.

POSTHERPETIC NEURALGIA

Herpes zoster-a vesicular skin eruption in dermatomal distribution, accompanied and followed by local pain and tenderness-is due to reactivation of varicella-zoster virus in patients with a history of varicella infection. It becomes increasingly common with advancing age (70% in those over 70 years), in immunocompromised patients, and in patients with certain malignant diseases (eg, leukemia, lymphoma). Postherpetic neuralgia is characterized by constant, severe, stabbing or burning, dysesthetic pain that may persist for months or years in a minority of patients, especially older ones. It occurs in the same dermatomic distribution as a previous bout of herpes zoster, conforming to the distribution of the involved nerve root, where residual scars may be present. When the head is involved, the first division of the trigeminal nerve is most commonly affected, so that pain is usually localized to the forehead on one side. Careful testing of the painful area reveals decreased cutaneous sensibility to pinprick. The other major complication of trigeminal herpes is decreased corneal sensation with impaired blink reflex, which can lead to corneal abrasion, scarring, and ultimate loss of vision.

The intensity and duration of the cutaneous eruption and the acute pain of herpes zoster are reduced by treatment with acyclovir, but this treatment has not been shown to lessen the likelihood of postherpetic neuralgia. Corti co steroids (60 mg/d prednisone, orally for 2 weeks, with rapid tapering) taken during the acute herpetic eruption also reduce the incidence of acute herpetic pain, but have an uncertain effect on postherpetic pain. Once the postherpetic pain syndrome is established, the most useful treatment has been with tricyclic antidepressants such as amitriptyline, 25-150 mg/d orally, which are thought to act directly on central nervous system pain-integration pathways (rather than via an antidepressant effect). Tricyclic antidepressant drugs may be more effective when combined with a phenothiazine, as in the commercially available preparation Triavil. Postherpetic neuralgia subsides within 6-12 months in many patients but in 50% of those over 70 years the pain persists. Lidocaine-prilocaine 2.5% cream, or lidocaine gel 5%, is effective topical therapy. Topical application of capsaicin cream, which depletes pain-mediating peptides from peripheral sensory neurons, can also be helpful but is poorly tolerated.

HYPERTENSION

Chronic hypertension is often invoked as a cause of headache, but evidence to support such a connection is sparse. In contrast, headache is a well-established complication of paroxysmal hypertension such as is seen in patients with pheochromocytoma or those ingesting tyramine-rich foods while being treated with monoamine oxidase inhibitors. In pheochromocytoma, headache attacks are brief. They last less than 15 minutes in one-half of patients and are characteristically associated with perspiration and tachycardia. The headache is usually bilateral and may be precipitated by urination if the bladder is involved.

ATYPICAL FACIAL PAIN

Constant, boring, mainly unilateral lower facial pain for which no cause can be found is referred to as atypical facial pain. Unlike trigeminal neuralgia, it is not confined to the trigeminal nerve distribution and is not paroxysmal. This idiopathic disorder must be distinguished from similar pain syndromes related to nasopharyngeal carcinoma, intracranial extension of squamous cell carcinoma of the face, or infection at the site of a tooth extraction. Treatment is with amitriptyline, 20-250 mg/d orally, alone or in combination with phenelzine, 30-75 mg/d orally. Dilantin can be an effective alternative, especially if a tricyclic is inappropriate.

CHRONIC HEADACHES

MIGRAINE

Migraine is manifested by headache that is usually unilateral and frequently pulsatile in quality; it is often associated with nausea, vomiting, photophobia, phonophobia and lassitude. Visual or other neurologic auras occur in about 10% of patients. Two-thirds to three-fourths of cases of migraine occur in women; the onset is early in life-approximately 25% beginning during the first decade, 55% by 20 years of age, and more than 90% before age 40. A family history of migraine is present in most cases.

Genetics of Migraine

The aggregation of migraine within families has long been recognized, although consistent mendelian patterns of inheritance have not been found among

the collective group of familial migraineurs. Presumably this reflects a variety of inheritance patterns, variable penetrance, and possibly multiple genes interacting with environmental factors in the multigenic/multifactorial pattern characteristic of complex diseases. Concordance rates in monozygotic twins of only 28-52 attest to the genetic component, but also predict a significant environmental contribution.

A rare subtype of migraine with aura, familial hemiplegic migraine, has a straightforward autosomal dominant, highly penetrant inheritance pattern indicative of a strong genetic component. Three genetic loci for familial hemiplegic migraine have been identified: one on Chr19p13 (associated with missense mutations in a brain-expressed, voltagegated P/Q calcium channel gene) and two neighboring loci on Chrlq.

Pathogenesis

Intracranial vasoconstriction and extracranial vasodilatation have long been held to be the respective causes of the aura and headache phases of migraine. This theory received support from the efficacy of vasoconstrictive ergot alkaloids (eg, ergotamine) in aborting the acute migraine attack and vasodilators such as amyl nitrite in abolishing the migraine aura. More recent studies of regional cerebral blood flow during migraine attacks have demonstrated a reduction in regional flow, which begins in the occipital region, during the aura phase. The "spreading depression" in cerebral blood flow, however, proceeds according to cytoarchitectural patterns in the cerebral cortex and does not reflect the distribution of major vascular territories. In addition, the areas of decreased blood flow do not correspond to the cortical areas responsible for the particular aura, and regional cerebral blood flow may remain depressed after focal neurologic symptoms have resolved and headache has begun. Later in the headache phase, blood flow increases to parts of the cortex (cingulate, auditory, and visual association areas) and the brainstem (serotonergic dorsal raphe nucleus and adrenergic nucleus ceruleus); treatment with effective agents (sumatriptan, ergotamine) attenuates the cortical but not brainstem changes. These data imply that vascular abnormalities in migraine may be secondary to a primary disturbance in neuronal function in the brainstem.

Serotonergic neurons ramify extensively throughout the brain, and many effective antimigraine drugs act as antagonists or partial agonists at central serotonin receptors. Serotonin in platelets decreases and urinary serotonin increases during the acute phase of a migraine attack. Depletion of serotonin by reserpine may precipitate migraine. The headache and other manifestations of migraine may thus reflect a disorder of central serotonergic neurotransmission. The link between neuronal initiation and trigeminovascular-mediated pain may be calcitonoin gene-related peptide (CGRP), which is a potent vasodilator increased in

venous blood during migraine and decreased by serotonin antagonists (sumatriptan).

Clinical Findings

A. Migraine with Aura (Classic Migraine). Classic migraine headache is preceded by transient neurologic symptoms-the aura. The most common auras are visual alterations, particularly hemianopic field defects and scotomas and scintillations that enlarge and spread peripherally. A throbbing unilateral headache ensues with or following these prodromal features. The frequency of headache varies, but more than 50% of patients experience no more than one attack per week. The duration of episodes is greater than 2 hours and less than 1 day in most patients. Remissions are common during the second and third trimesters of pregnancy and after menopause. Especially in the elderly, prodromal symptoms may occur without headache (migraine equivalents). Although hemicranial pain is a hallmark of classic migraine, headaches can also be bilateral. Bilateral headache, therefore, does not exclude the diagnosis of migraine, nor does an occipital location-a characteristic commonly attributed to tension headaches. During the headache, prominent associated symptoms include nausea, vomiting, photophobia, phonophobia, irritability, osmophobia, and lassitude. Uncommonly, migraines are associated with frank neurologic deficits that accompany, or persist beyond resolution of, the pain phase. These may include hemiparesis, hemisensory loss, speech dysfunction, or visual disturbance. Vasomotor and autonomic symptoms are frequent; light-headedness, vertigo, ataxia, or altered consciousness may represent vertebrobasilar ischemia. All these phenomena may be distinguished from stroke both by their gradual onset ("migrainous march") and spontaneous resolution. Stroke may very exceptionally occur as a consquence of migraine alone.

B. Migraine without Aura (Common Migraine). The common migraine headache lacks the classic aura, is usually bilateral and periorbital, and is seen more frequently in clinical practice. The pain may be described as throbbing. As the pain persists, associated cervical muscle contraction can compound the symptoms. Scalp tenderness is often present during the episode. Vomiting may occasionally terminate the headache.

A useful bedside test for both common and classic migraine is reducing headache severity by compressing the ipsilateral carotid or superficial temporal artery.

Precipitating Factors

Migraine attacks can be precipitated by certain foods (tyramine-containing cheeses; meat, such as hot dogs or bacon, with nitrite preservatives; chocolate containing phenylethylamine but not chocolate alone) and by food ad-

ditives such as monosodium glutamate, a commonly used flavor enhancer. Fasting, emotion, menses, drugs (especially oral contraceptive agents and vasodilators such as nitroglycerin), and bright lights may also trigger attacks.

Treatment

Acute migraine attacks may respond to simple analgesics (eg, aspirin, acetaminophen, naprosyn). If not, they usually respond to ergot preparations or to the 5-HT agonist sumatriptan. These drugs must be taken immediately at the onset of symptoms to be maximally effective. Rapidly absorbed forms (eg, suppository, aerosol) are superior to oral or sublingual preparations. In severe cases, subcutaneous, nasal, intramuscular or intravenous administration is used. Unfortunately, nausea, which is a prominent feature of migraine, is also a common side effect of the drugs, so that concomitant administration of an antiemetic (eg, metoclopramide, 10 mg subcutaneously or intravenously) may be necessary. Ergot alkaloids and 5-HT agonists are potent vasoconstrictors and are contraindicated in patients with significant hypertension or cardiac disease. Established migraine headaches may respond to dihydroergotamine, sumatriptan, or narcotic analgesics (eg, meperidine, 100 mg intramuscularly).

Several drugs are effective in the prophylactic treatment of migraine. Prophylactic treatment is indicated for patients who have frequent attacks – especially more than one per week – and those for whom the ergot alkaloids used for acute treatment are poorly tolerated or contraindicated. Three structurally unrelated agents – propranolol, amitriptyline, and valproic acid – are the mainstays of therapy. Each is effective in a substantial fraction of patients, and patients refractory to one agent may respond to another. The initial choice of medication is usually influenced by consideration of clinical side effects that may be especially troublesome for a particular patient. Propranolol, imipramine, and amitriptyline may be sedating, especially at the onset of treatment. The β-adrenergicreceptor-blocking properties of propranolol often preclude its use in patients with congestive heart failure, asthma, or insulin-dependent diabetes. It may also be associated with depression, hypotension, exercise intolerance, and impotence. The anticholinergic actions of amitriptyline may complicate glaucoma and prostatism. Valproic acid should be introduced gradually as nausea can be a problem; it is also particularly contraindicated in pregnancy.

Calcium channel antagonists such as verapamil or nicardepine are also efficacious in the prophylactic treatment of migraine. Drugs available in other countries or approved in the United States only for other indications include nimodipine and flunarizine; however, both common and classic migraine respond to these drugs. As discussed above, potential side effects should be taken into account in the choice of therapy. Verapamil, which has pronounced effects on cardiac and gastrointestinal calcium channels, may exacerbate atrioventricular nodal heart block and congestive heart failure and frequently causes constipa-

tion. Nimodipine, which is more selective for vascular smooth muscle, is associated with a higher incidence of headache, light-headedness, hypotension, and peripheral edema. It should not be used in conjuction with β-blockers. Nifedipine is ineffective. Surprisingly, selective serotonin reuptake inhibitors have not been shown to be efficacious.

Migraine during pregnancy should be treated only with opiates, eg, meperidine 100-150 mg orally, as all other pharmacologic agents raise concerns regarding teratogenicity or complications of pregnancy.

ANALGESIC WITHDRAWAL HEADACHE

A common, frequently unsuspected, cause of intractable headache is overuse of analgesics. The patient, in futile attempts at relief, takes increasing amounts of medications (both prescription and over-the-counter drugs). When the high blood levels drop, even slightly, the headache rebounds; the result is daily, virtually constant, atypical headache, which may be superimposed on an underlying migraine pattern. Caffeine-containing analgesics are particularly responsible. The patient should be abruptly withdrawn from all such medications and caffeine. After a few weeks of withdrawal symptoms the underlying, usually less severe, headache pattern will reveal itself and can be more appropriately treated.

CLUSTER HEADACHE

Cluster headache is a common headache syndrome seen much more frequently in men than in women. Cluster headaches characteristically begin at a later age than does migraine, with a mean age at onset of 25 years. There is rarely a family history of such headaches. The syndrome presents as clusters of brief, very severe, unilateral, constant nonthrobbing headaches that last from 10 minutes to less than 2 hours. Unlike migraine headaches, cluster headaches are always unilateral, and usually recur on the same side in any given patient. The headaches commonly occur at night, awakening the patient from sleep, and recur daily, often at nearly the same time of day, for a cluster period of weeks to months. Between clusters, the patient may be free from headaches for months or years.

The headache may begin as a burning sensation over the lateral aspect of the nose or as a pressure behind the eye. Ipsilateral conjunctival injection, lacrimation, nasal stuffiness, and Homer's syndrome are commonly associated with the attack. Episodes are often precipitated by the use of alcohol or vasodilating drugs. During a cluster siege, individual attacks may be precipitated by alcohol.

At the onset of a headache cluster, treatment involves measures both to abort the acute attack and to prevent subsequent ones. Acute relief of pain within minutes may be achieved by sumatriptan, 100% oxygen (8-10 L/min for 10-15 minutes), or dihydroergotamine.

Several drugs used in the treatment of migraine, including 5-HT agonists, ergotamine, dihydroergotamine, methysergide, and calcium channel antagonists (verapamil, sustained-released), are also useful for preventing recurrent symptoms during an active bout of cluster headache. Ergotamine rectal suppositories or subcutaneous dihydroergotamine at bed-time may be especially helpful for nocturnal headaches. In addition, dramatic improvement is typically seen with administration of prednisone, 40-80 mg/d orally for I week, discontinued by tapering the dose over the following week. Pain may resolve within hours, and most patients who respond do so within 2 days. Alternatively, lithium carbonate or lithium citrate syrup, 300 mg orally three times daily, is highly effective in many cases. Serum lithium levels should be measured at weekly intervals for the first several weeks to reduce the likelihood of adverse effects. These include disorders of the gastrointestinal (nausea, diarrhea), urinary (polyuria, renal failure), endocrine (hypothyroidism), and nervous systems (tremor, dysarthria, ataxia, myoclonus, seizures). Chronic rather than episodic cluster headaches may respond dramatically to indomethacin, 25 mg three times daily. A bilateral variant, hypnic headache, lacking the autonomic components, occurs in the elderly. It is responsive to lithium.

TENSION-TYPE HEADACHE

Tension headache is the term used to describe chronic headaches of inapparent cause that lack features characteristic of migraine or cluster headache. The underlying pathophysiologic mechanism is unknown, and tension is unlikely to be primarily responsible. Contraction of neck and scalp muscles, which has also been proposed as the cause, is probably a secondary phenomenon. In its classic form, tension headache is a chronic disorder that begins after age 20. It is characterized by frequent (often daily) attacks of nonthrobbing, bilateral occipital head pain that is not associated with nausea, vomiting, or prodromal visual disturbance. The pain is sometimes likened to a tight band around the head. Women are more commonly affected than men. Although tension headache and migraine have been traditionally considered distinct disorders, many patients have headaches that exhibit features of both. Thus, some patients who are classified as having tension headaches experience throbbing headaches, unilateral head pain, or vomiting with attacks. In consequence, it may be more accurate to view tension headache and migraine as representing opposite poles of a single clinical spectrum.

Drugs used in the treatment of tension headache include many of the same agents used for migraine. Acute attacks may respond to aspirin, other nonsteroidal anti-inflammatory drugs, acetaminophen, ergotamine, or dihydroergotamine. For prophylactic treatment, amitriptyline, imipramine, or selective serotonin reuptake inhibitors (eg, sertraline or fluoxetine) are often effective, and propranolol is useful in some cases. Although many patients respond to benzodiazepines such as diazepam, 5-30 mg/d orally, or chlordiazepoxide, 10-75 mg/d orally, these drugs should be used sparingly because of their addictive potential. Psychotherapy, physical therapy, and relaxation techniques can provide additional benefit in selected cases.

ICE PICK PAIN

Very brief, sharp, severe pains located in the scalp outside of the trigeminal distribution are named by their defining characteristic as "ice pick pains." They may be single or repetitive or occur in clusters, either at a single point or scattered over the scalp. The pains are electric-like jabs maximal in intensity in less than a second and then resolving rapidly; they are severe enough to cause involuntary flinching. They are more common in migraine and cluster patients, but occur in some headache-free individuals as well. Patients frequently seek medical attention because of the intensity of the pain. If the bouts of pain are repetitive, treatment may be indicated; the syndrome responds to indomethacin (25 mg three times daily).

CERVICAL SPINE DISEASE

Injury or degenerative disease processes involving the upper neck can produce pain in the occiput or referred to the orbital regions. The most important source of discomfort is irritation of the second cervical nerve root. In the lower cervical spine, disk disease or abnormalities of the articular processes refer pain to the ipsilateral arm or shoulder, not to the head. Cervical muscle spasm may occur, however. Acute pain of cervical origin is treated with immobilization of the neck (eg, using a soft collar) and analgesics or anti-inflammatory drugs.

SINUSITIS

Acute sinusitis can produce pain and tenderness localized to the affected frontal or maxillary sinus areas. Inflammation in the ethmoidal or sphenoidal sinuses produces a deep midline pain behind the nose. Sinusitis pain is increased by bending forward and by coughing or sneezing. Tenderness and accentuation

of pain on percussion over the frontal or maxillary area are present on examination. Sinusitis is treated with vasoconstrictor nose drops (eg, phenylephrine, 0.25%, instilled every 2-3 hours), antihistamines, and antibiotics. In refractory cases, sinus drainage may be necessary. Patients who complain of chronic sinus headache rarely have recurrent inflammation of the sinuses; they are much more likely to have migraine or tension headaches.

DENTAL DISEASE

Temporomandibular joint dysfunction is a poorly defined syndrome that is characterized by preauricular facial pain, limitation of jaw movement, tenderness of the muscles of mastication, and "clicking" of the jaw with movement. Symptoms are often associated with malocclusion, bruxism, or clenching of the teeth, and may result from spasm of the masticatory muscles. Some patients benefit from local application of heat, jaw exercises, nocturnal use of a bite guard, or nonsteroidal antiinflammatory drugs.

Infected tooth extraction sites can also give rise to pain, which is characteristically constant, unilateral, and aching or burning in character. Although radiologic studies may be normal, injection of a local anesthetic at the extraction site relieves the symptoms. Treatment is with jaw bone curettage and antibiotics.

MENINGITIS & ENCEPHALITIS

BACTERIAL MENINGITIS

Bacterial meningitis is a leading cause of acute confusional states and one in which early diagnosis greatly improves the outcome. Conditions that predispose patients to its development include systemic (especially respiratory) or parameningeal infection, head trauma, anatomic meningeal defects, previous neurosurgical procedures, cancer, alcoholism, and other immunodeficiency states. The etiologic organism varies with age and with the presence of predisposing conditions.

Pathogenesis

Bacteria typically gain access to the central nervous system by colonizing the mucous membranes of the nasopharynx, leading to local tissue invasion, bacteremia, and hematogenous seeding of the subarachnoid space. Bacteria can also spread to the meninges directly, through anatomic defects in the skull or from parameningeal sites such as the paranasal sinuses or middle ear. Polysaccharide bacterial capsules, lipopolysaccharides, and outer membrane proteins may contribute to the bacterial invasion and virulence. Low levels of antibody and complement in the subarachnoid space are inadequate to contain the infection. The resulting inflammatory response is associated with the release of inflammatory cytokines, including interleukins 1 and 6 and tumor necrosis factor a, that promote blood-brain barrier permeability, vasogenic cerebral edema, changes in cerebral blood flow, and perhaps direct neuronal toxicity.

Pathologically, bacterial meningitis is characterized by leptomeningeal and perivascular infiltration with polymorphonuclear leukocytes and an inflammatory exudate. These changes tend to be most prominent over the cerebral convexities in *Streptococcus pneumoniae* and *Haemophilus* infection and over the base of the brain when *Neisseria meningitidis* is the causative organism. Brain edema, hydrocephalus, and cerebral infarction may occur, although actual bacterial invasion of the brain is rare.

Clinical Findings

A. Symptoms and Signs. At the time of presentation, most patients have experienced symptoms of meningitis for one to seven days. The symptoms include fever, confusion, vomiting, headache, and neck stiffness, but the full syndrome is often not present.

Physical examination may show fever and signs of systemic or parameningeal infection, such as skin abscess or otitis. A petechial rash is seen in 50-

60% of patients with *N meningitidis* meningitis. Signs of meningeal irritation are seen in about 80% of cases; they are often absent at the extremes of age or with profoundly impaired consciousness. The level of consciousness, when altered, ranges from mild confusion to coma. Focal neurologic signs, seizures, and cranial nerve palsies may occur.

B. Laboratory Findings. Blood counts may reveal polymorphonuclear leukocytosis related to systemic infection or leukopenia reflecting immunosuppression. In associated bacteremia, the causative organism can be cultured from the blood in 40-90% of cases. X-rays of the chest, sinuses, or mastoid bones may indicate a primary site of infection. A brain CT scan may show contrast enhancement of the cerebral convexities, the base of the brain, or the ventricular ependyma. The EEG is usually diffusely slowed, and focal abnormalities suggest the possibility of focal cerebritis, abscess formation, or scarring.

While these studies are helpful in some cases, the essential investigation in all cases of suspected meningitis is prompt lumbar puncture and CSF examination. CSF pressure is elevated in about 90% of cases, and the appearance of the fluid ranges from slightly turbid to grossly purulent. CSF white cell counts of 1000-10,000/μL are usually seen, consisting chiefly of polymorphonuclear leukocytes, although mononuclear cells may predominate in *Listeria monocytogenes* meningitis. Protein concentrations of 100-500 mg/dL are most common. The CSF glucose level is lower than 40 mg/dL in about 80% of cases; it may be immeasurably low. Gram-stained smears of CSF identify the causative organism in 70-80% of cases. CSF culture, which is positive in about 80% of cases, provides a definitive diagnosis and allows determination of antibiotic sensitivity. The polymerase chain reaction, which amplifies viral DNA, has also been used with CSF specimens to diagnose bacterial meningitis, including *H influenzae, N meningitidis,* and *L monocytogenes* meningitis.

Differential Diagnosis

The signs of meningeal irritation may also be seen with subarachnoid hemorrhage, but the distinction is easily made when lumbar puncture shows bloody CSF. Early viral meningitis can produce polymorphonuclear pleocytosis and symptoms identical to those of bacterial meningitis, but a repeat lumbar puncture after 6-12 hours should demonstrate a shift to lymphocytic predominance, and the CSF glucose level is normal.

Prevention

Children should be routinely immunized against *H influenzae* by vaccination. A vaccine is also available for some strains of *N meningitidis* and is recommended for travelers to areas of ongoing epidemics. The risk of contracting *H influenzae* or *N meningitidis* meningitis can be reduced in household and other close contacts of affected patients by the prophylactic administration of ri-

fampin, 20 mg/kg/d orally, given as a single daily dose for 4 days *(H influenzae)* or as two divided doses for 2 days *(N meningitidis).*

Treatment

Unless the physical examination shows focal neurologic abnormalities or papilledema, lumbar puncture should be performed immediately; if the CSF is not clear and colorless, antibiotic treatment (see below) is started without delay. When focal signs or papilledema are present, blood and urine should be taken for culture, antibiotics begun, and a brain CT scan obtained. If the scan shows no focal lesion that would contraindicate lumbar puncture, the puncture is then performed. The initial choice of antibiotics is empirical, based upon the patient's age and predisposing factors.

Therapy is adjusted as indicated when the Gram's stain or culture and sensitivity results become available. Lumbar puncture can be repeated to assess the response to therapy. CSF should be sterile after 24 hours, and a decrease in pleocytosis and the proportion of polymorphonuclear leukocytes should be apparent within 3 days.

The use of corticosteroids as an adjunct to antibiotic treatment of bacterial meningitis is controversial, and is based primarily on their ability to reduce hearing loss and neurologic sequelae in children with *H influenzae* meningitis. Nonetheless, some authorities recommend dexamethasone, 0.15 mg/kg intravenously every 6 hours for the first 4 days of antibiotic therapy in children under 2 months of age, and in adults with a positive Gram's stain and increased intracranial pressure.

Prognosis

Complications of bacterial meningitis include headache, seizures, hydrocephalus, inappropriate secretion of antidiuretic hormone, residual neurologic deficits (including cognitive disturbances and cranial – especially VIII – nerve abnormalities), and death. A CT scan will confirm suspected hydrocephalus. Fluid and electrolyte status should be carefully monitored in patients with meningitis. *N meningitidis* infections may be complicated by adrenal hemorrhage related to meningococcemia, resulting in hypotension and often death (Waterhouse-Friderichsen syndrome).

The morbidity and mortality rates of bacterial meningitis are high. Fatalities occur in about 20% of affected adults, but fatality rates are higher with some pathogens (eg, S *pneumoniae,* gram-negative bacilli) than others (eg, *H influenzae, N meningitidis).* Factors that worsen prognosis include extremes of age, delays in diagnosis and treatment, a complicating illness, stupor or coma, seizures, and focal neurologic signs.

TUBERCULOUS MENINGITIS

Tuberculous meningitis is an important diagnostic consideration in patients who present with a confusional state, especially if there is a history of pulmonary tuberculosis, alcoholism, corticosteroid treatment, HIV infection, or other conditions associated with impaired immune responses. It should also be considered if patients are from areas (eg, Asia, Africa) or groups (eg, the homeless and inner-city drug users) with a high incidence of tuberculosis. Tuberculous meningitis usually results from reactivation of latent infection with *Mycobacterium tuberculosis.* Primary infection, typically acquired by inhaling bacillus-containing droplets, may be associated with metastatic dissemination of blood-borne bacilli from the lungs to the meninges and the surface of the brain. Here the organisms remain in a dormant state in tubercles that can rupture into the subarachnoid space at a later time, resulting in tuberculous meningitis.

Pathology

The principal neuropathologic finding is a basal meningeal exudate containing mainly mononuclear cells. Tubercles may be seen on the meninges and surface of the brain. The ventricles may be enlarged as a result of hydrocephalus, and their surfaces may show ependymal exudate or granular ependymitis. Arteritis can result in cerebral infarction, and basal inflammation and fibrosis can compress cranial nerves.

Clinical Findings

A. Symptoms and Signs. Symptoms have usually been present for less than 4 weeks at the time of presentation and include fever, lethargy or confusion, and headache. Weight loss, vomiting, neck stiffness, visual impairment, diplopia, focal weakness, and seizures may also be noted. A history of contact with known cases of tuberculosis is usually absent.

Fever, signs of meningeal irritation, and a confusional state are the most common findings on physical examination, but all may be absent. Papilledema, ocular palsies, and hemiparesis are sometimes seen. Complications include spinal subarachnoid block, hydrocephalus, brain edema, cranial nerve palsies, and stroke caused by vasculitis or compression of blood vessels at the base of the brain.

B. Laboratory Findings. Only about one-half to two-thirds of patients show a positive skin test or evidence of active or healed tubercular infection on chest x-ray. The only investigation that can establish the diagnosis is CSF analysis. CSF pressure is usually increased, and the fluid is typically clear and colorless but may form a clot upon standing. Lymphocytic and mononuclear cell pleocytosis of 50-500 cells/μL is most often seen, but polymorphonuclear pleocytosis can occur early and may give an erroneous impression of bacterial meningitis. CSF protein is usually more than 100 mg/dL and may exceed 500

mg/dL, particularly in patients with spinal subarachnoid block. The glucose level is usually decreased and may be less than 20 mg/dL. A decreased chloride level, formerly thought to be specifically associated with tuberculous meningitis, is no longer considered diagnostically useful. Acid-fast smears of CSF should be performed in all cases of suspected tuberculous meningitis, but they are positive in only a minority of cases. Definitive diagnosis is most often made by culturing *M tuberculosis* from the CSF, a process that usually takes several weeks and requires large quantities of spinal fluid for maximum yield. However, the polymerase chain reaction has also been used for diagnosis. Finally, the CT scan may show contrast enhancement of the basal cisterns and cortical meninges, or hydrocephalus.

Differential Diagnosis

Many other conditions can cause a subacute confusional state associated with mononuclear cell pleocytosis, including syphilitic, fungal, neoplastic, and partially treated bacterial meningitis. These can be diagnosed by appropriate smears, cultures, and serologic and cytologic examinations.

Treatment

Treatment should be started as early as possible; it should not be withheld while awaiting culture results. The decision to treat is based on the CSF findings described above; lymphocytic pleocytosis and decreased glucose are particularly suggestive, even if acid-fast smears are negative. Four drugs are used for initial therapy, until culture and susceptibility test results are known. These are isoniazid, 300 mg; rifampin, 600 mg; pyrazinamide, 25 mg/kg; and ethambutol, 15 mg/kg, each given orally once daily. For susceptible strains, ethambutol can be discontinued, and triple therapy continued for 2 months, followed by 4-10 months of treatment with isoniazid and rifampin alone. Corticosteroids (eg, prednisone, 60 mg/d orally in adults or 1-3 mg/kg/d orally in children, tapered gradually over 3-4 weeks) are indicated as adjunctive therapy in patients with spinal subarachnoid block. They may also be indicated in seriously ill patients with focal neurologic signs or with increased intracranial pressure from cerebral edema. The risk of using corticosteroids may be high, however, especially if tuberculous meningitis has been mistakenly diagnosed in a patient with fungal meningitis. Therefore, if fungal meningitis has not been excluded, antifungal therapy (see below) should be added, together with corticosteroids. Pyridoxine, 50 mg/d, can be used to decrease the likelihood of isoniazid-induced polyneuropathy. Complications of therapy include hepatic dysfunction (isoniazid, rifampin, and pyrazinamide), polyneuropathy (isoniazid), optic neuritis (ethambutol), seizures (isoniazid), and ototoxicity (streptomycin).

Prognosis

Even with appropriate treatment, about one-third of patients with tubercu-

lous meningitis succumb. Coma at the time of presentation is the most significant predictor of a poor prognosis.

SYPHILITIC MENINGITIS

Acute or subacute syphilitic meningitis usually occurs within 2 years after primary syphilitic infection. It is most common in young adults, affects men more often than women, and requires prompt treatment to prevent the irreversible manifestations of tertiary neurosyphilis. In about one-fourth of patients with *Treponema pallidum* infection, treponemes gain access to the central nervous system, where they produce a meningitis that is usually asymptomatic (asymptomatic neurosyphilis). Asymptomatic invasion of the central nervous system is associated with CSF pleocytosis, elevated protein, and positive serologic tests for syphilis.

Clinical Findings

A. Symptoms and Signs. In a few patients, syphilitic meningitis is a clinically apparent acute or subacute disorder. At the time of presentation, symptoms such as headache, nausea, vomiting, stiff neck, mental disturbances, focal weakness, seizures, deafness, and visual impairment have usually been present for up to 2 months.

Physical examination may show signs of meningeal irritation, confusion or delirium, papilledema, hemiparesis, and aphasia. The cranial nerves most frequently affected are (in order) the facial (VII), acoustic (VIII), oculomotor (III), trigeminal (V), abducens (VI), and optic (II) nerves, but other nerves may be involved as well. Fever is typically absent.

B. Laboratory Findings. The diagnosis is established by CSF findings. Opening pressure is normal or slightly elevated. Pleocytosis is lymphocytic or mononuclear in character, with white cell counts usually in the range of 100-1000/μL. Protein may be mildly or moderately elevated (<200 mg/dL) and glucose mildly decreased. CSF VDRL and serum FT A or MHA-TP tests are usually positive. Protein electrophoretograms of CSF may show discrete gamma globulin bands (oligoclonal bands) not visible in normal CSF.

Treatment

Acute syphilitic meningitis is usually a self-limited disorder with no or minimal sequelae. Subsequent development of more advanced manifestations of neurosyphilis, including vascular and parenchymatous disease (eg, tabes dorsalis, general paresis, optic neuritis, myelitis), can be prevented by adequate treatment of the early syphilitic infection.

Syphilitic meningitis is treated with aqueous penicillin G, 2-4 x 10^6 units intravenously every 4 hours for 10 days. For penicillin-allergic patients, tetracy-

cline or erythromycin, 500 mg orally every 6 hours for 20 days, can be substituted. The CSF should be examined every 6 months until all findings are normal. Another course of therapy must be given if the CSF cell count or protein remains elevated.

LYME DISEASE

Lyme disease is a tick-borne disorder that results from systemic infection with the spirochete *Borrelia burgdorferi.* The disease occurs in Europe, the northeastern and western United States, and Australia; most cases occur during the summer months. Primary infection may be manifested by an expanding erythematous annular skin lesion (erythema migrans) that usually appears over the thigh, groin, or axilla. Less distinctive symptoms include fatigue, headache, fever, neck stiffness, joint or muscle pain, anorexia, sore throat, and nausea. Neurologic involvement may be delayed for up to 10 weeks and is characterized by meningitis or meningoencephalitis and disorders of the cranial or peripheral nerves or nerve roots. Cardiac abnormalities (conduction defects, myocarditis, pericarditis, cardiomegaly, or heart failure) can also occur at this stage. Lyme meningitis usually produces prominent headache that may be accompanied by signs of meningeal irritation, photophobia, pain when moving the eyes, nausea, and vomiting. When encephalitis is present, it is usually mild and characterized by insomnia, emotional lability, or impaired concentration and memory. The CSF usually shows a lymphocytic pleocytosis with 100-200 cells/μL, slightly elevated protein, and normal glucose. Oligoclonal IgG bands may be detected. Definitive diagnosis is usually made by serologic testing for *B burgdorferi,* preferably by enzyme-linked immunosorbent assay (ELISA) followed by Western blot, but the polymerase chain reaction, which can amplify spirochetal DNA in synovial fluid, blood, or CSF, has also been used. For patients with Bell's palsy, treatment is with doxycycline (100 mg twice daily), tetracycline (500 mg four times daily), or amoxacillin (250-500 mg three times daily), each given orally for 1 month. With meningitis of other CNS involvement, intravenous treatment is indicated with ceftriaxone (2 g intravenously daily), penicillin G (20 million units intravenously daily in six divided doses), or cefotaxime (2 g intravenously every 8 hours), continued for 3-4 weeks. Symptoms typically resolve within 10 days in treated cases. Untreated or inadequately treated infections may lead to recurrent oligoarthritis, and chronic neurologic disorders including memory, language, and other cognitive disturbances; focal weakness; and ataxia. In such cases, a CT scan or MRI may show hydrocephalus, lesions in white matter resembling those seen in multiple sclerosis, or abnormalities suggestive of cerebral infarction. Subtle chronic cognitive or behavioral symptoms should not be attributed to Lyme encephalitis in the absence of serologic evidence of *B burgdorferi* exposure, CSF abnormalities, or focal neurologic signs.

VIRAL MENINGITIS & ENCEPHALITIS

Viral infections of the meninges (meningitis) or brain parenchyma (encephalitis) often present as acute confusional states. Children and young adults are frequently affected. Viral meningitis is most often caused by enteric viruses. Although the etiologic agent is not identified in most cases of viral encephalitis, childhood exanthems, arthropodborne agents, and herpes simplex type 1 are the more commonly recognized causes.

Pathology

Viral infections can involve the central nervous system in three ways, through hematogenous dissemination of systemic viral infection (eg, arthropodborne viruses); the neuronal spread of the virus (eg, herpes simplex, rabies) by axonal transport; and autoimmune responses causing postinfectious demyelination (eg, varicella, influenza).

Pathologic changes in viral meningitis consist of an inflammatory meningeal reaction mediated by lymphocytes. Encephalitis is characterized by perivascular cuffing, lymphocytic infiltration, and microglial proliferation mainly involving subcortical gray matter regions. Intranuclear or intracytoplasmic inclusions are often seen.

Clinical Findings

A. Symptoms and Signs. Clinical manifestations of viral meningitis include fever, headache, neck stiffness, photophobia, pain with eye movement, and mild impairment of consciousness. Patients usually do not appear as ill as those with bacterial meningitis. Systemic viral infection may be reflected by skin rash, pharyngitis, lymphadenopathy, pleuritis, carditis, jaundice, organomegaly, diarrhea, or orchitis. Such associations often suggest a particular etiologic agent. Because viral encephalitis involves the brain directly, marked alterations of consciousness, seizures, and focal neurologic signs can occur. When signs of meningeal irritation and brain dysfunction coexist, the condition is termed meningoencephalitis.

B. Laboratory Findings. CSF analysis is the most important laboratory investigation. CSF pressure is normal or increased, and a lymphocytic or monocytic pleocytosis is present, with cell counts usually less than 1000/μL. (Higher counts can be seen in lymphocytic choriomeningitis or herpes simplex encephalitis.) A polymorphonuclear pleocytosis can occur early in viral meningitis, while red blood cells may be seen with herpes simplex encephalitis. Protein is normal or slightly increased (usually 80-200 mg/dL). Glucose is usually normal; it may be decreased in mumps, herpes zoster, or herpes simplex encephalitis. Gram's stains and bacterial, fungal, and acid-fast bacillius (AFB) cultures are

negative. Oligoclonal bands and CSF protein electrophoresis abnormalities may be present. An etiologic diagnosis can often be made by virus isolation or by acute- and convalescent-phase CSF antibody titers.

Blood counts may show a normal white cell count, leukopenia, or mild leukocytosis. Atypical lymphocytes in blood smears and a positive heterophil (Monospot) test suggest infectious mononucleosis. Serum amylase is frequently elevated in mumps; abnormal liver function tests are associated with both hepatitis viruses and infectious mononucleosis. The EEG is diffusely slowed, especially if there is direct cerebral involvement; more characteristic findings can be found in encephalitis caused by herpes simplex infection.

Differential Diagnosis

The differential diagnosis of meningitis with mononuclear cell pleocytosis includes partially treated bacterial meningitis as well as syphilitic, tuberculous, fungal, parasitic, neoplastic, and other meningitides. Evidence of systemic viral infection and CSF wet mounts, stained smears, cultures, and cytologic examination can distinguish among these possibilities. When presumed early viral meningitis is associated with a polymorphonuclear pleocytosis of less than 1000 white blood cells/μL and normal CSF glucose, one of two strategies can be used. The patient can be treated for bacterial meningitis until the results of CSF cultures are known, or treatment can be withheld and lumbar puncture repeated in 6-12 hours. If the meningitis is viral in origin, the second sample should show a mononuclear cell pleocytosis. The syndrome of viral encephalitis may clinically resemble that from metabolic disorders, but it can be distinguished by spinal fluid findings.

A disorder that may be clinically indistinguishable from viral encephalitis is the immune-mediated encephalomyelitis that may follow viral infections such as influenza, measles, or chickenpox. Progressive neurologic dysfunction typically begins a few days after the viral illness but can also occur either simultaneously or up to several weeks later. Neurologic abnormalities result from perivenous demyelination, which often severely affects the brain stem. The CSF shows a lymphocytic pleocytosis, usually with cell counts of 50-150/μL, and mild protein elevation.

Treatment

Except for herpes simplex encephalitis, which is discussed separately (see below), no specific therapy for viral meningitis and encephalitis is available. Corticosteroids are of no benefit except in immune-mediated postinfectious syndromes. Headache and severe hyperthermia can be treated with acetaminophen; mild fever requires no treatment and may even contribute to the host response to the virus. Seizures usually respond to phenytoin or phenobarbital. Supportive measures in comatose patients include mechanical ventilation and intravenous or nasogastric feeding.

Prognosis

Symptoms of viral meningitis usually resolve spontaneously within 2 weeks regardless of the causative agent, although residual deficits may be seen. The outcome of viral encephalitis varies with the specific virus, however; eastern equine and herpes simplex virus infections are associated with severe morbidity and high mortality rates. Mortality rates as high as 20% have also been reported in immune-mediated encephalomyelitis following measles infections.

HERPES SIMPLEX VIRUS (HSV) ENCEPHALITIS

Specific antiviral therapy is available for this disorder, which is the most common type of sporadic fatal encephalitis in the United States. About two-thirds of cases involve patients over 40 years of age. Primary herpes infections most often present as stomatitis (HSV type 1) or a venereally transmitted genital eruption (HSV type 2). The virus migrates along nerve axons to sensory ganglia, where it persists in a latent form – and may be subsequently reactivated. It is not clear whether HSV type 1 encephalitis, the most common type in adults, represents a primary infection or a reactivation of latent infection. Neonatal HSV encephalitis usually results from acquisition of type 2 virus during passage through the birth canal of a mother with active genital lesions. Central nervous system involvement by HSV type 2 in adults usually causes meningitis, rather than encephalitis.

Pathology

The pathologic picture of HSV type 1 encephalitis is that of an acute, necrotizing, asymmetric hemorrhagic process with lymphocytic and plasma cell reaction, which usually involves the medial temporal and inferior frontal lobes. Intranuclear inclusions may be seen in the neurons and glia. In patients who recover, the chronic state is characterized by cystic necrosis of the involved regions.

Clinical Findings

A. Symptoms and Signs. The clinical syndrome may include headache, stiff neck, vomiting, behavioral disorders, memory loss, anosmia, aphasia, hemiparesis, and focal or generalized seizures. Active herpes labialis is seen occasionally, but its presence does not increase the likelihood that the encephalitis is due to HSV. The encephalitis is usually rapidly progressive over several days and may result in coma or death. The most common sequelae in patients who survive HSV encephalitis are memory and behavior disturbances, reflecting the predilection of the process for limbic structures.

B. Laboratory Findings. The CSF in HSV type 1 encephalitis most often shows increased pressure, lymphocytic or mixed lymphocytic and polymorphonuclear pleocytosis (50-100 white blood cells/μL), mild protein elevation, and normal glucose. Red blood cells, xanthochromia, and decreased glucose are seen in some cases. The virus generally cannot be isolated from the CSF, but viral DNA has been detected by the polymerase chain reaction in some cases. The EEG may show periodic slow-wave complexes arising from one or both temporal lobes, and CT scans and MRI may show abnormalities in one or both temporal lobes. These can extend to frontal or parietal regions and are sometimes enhanced with the infusion of contrast material. It should be noted that imaging studies may also be normal. Definitive diagnosis is typically made by biopsy of affected brain areas, with the choice of biopsy site guided by the EEG, CT, or MRI findings.

Differential Diagnosis

The symptoms and signs are not specific for herpes virus infection. The greatest diagnostic difficulty is distinguishing between HSV encephalitis and brain abscess. The latter is suggested by systemic bacterial infection, a slower progression of deficits, less-marked CSF pleocytosis, a continuous polymorphic slow-wave disturbance in the EEG, and symmetric contrast enhancement of the rim of the lesion seen on CT scan. The two disorders often cannot be differentiated on clinical grounds alone, however. Final diagnoses in patients undergoing brain biopsy for suspected HSV encephalitis have included vasculitis, other viral infections, bacterial abscess, fungal infections, tumor, Reye's syndrome, parasitic infections, and tuberculosis. Because many of these conditions require specific therapy and none are favorably affected by the treatment used for HSV encephalitis, some clinicians argue that all patients with suspected HSV encephalitis should undergo brain biopsy to establish a definitive diagnosis. The most commonly accepted approach, however, is to treat patients with probable HSV encephalitis as described below and to reserve biopsies for those who fail to improve.

Treatment

The most effective drug is acyclovir, given intravenously at a dosage of 30 mg/kg/d, divided into three daily doses, each given over 1 hour. Treatment is continued for 14-21 days. Complications reported include erythema at the intravenous infusion site, gastrointestinal disturbances, headache, skin rash, tremor, seizures, and encephalopathy or coma. Treatment is started as early as possible, since outcome is greatly influenced by the severity of dysfunction at the time treatment is initiated. Treatment is discontinued if a subsequent brain biopsy establishes another diagnosis.

Prognosis

Prognosis is influenced by the patient's age and level of consciousness at presentation and by the treatment. Patients under the age of 30 years and those who are only lethargic at the onset of treatment are more likely to survive than are older or comatose patients. Reported mortality rates are 44% at six months in vidarabine-treated patients and 28% at 18 months in patients given acyclovir. Acyclovir also increases the fraction of patients with no or only minor neurologic sequelae from 5% to 38%, compared with vidarabine. It is not known whether a combination of acyclovir and vidarabine has greater efficacy than either drug used alone.

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

AIDS is a disorder caused by systemic infection with human immunodeficiency virus-l (HIV-l) and characterized by opportunistic infections, malignant neoplasms (typically non-Hodgkin's lymphoma or Kaposi's sarcoma), and a variety of neurologic disturbances. Transmission occurs through sexual activity or by transfer of virus-contaminated blood or blood products. Individuals at particular risk of infection include homosexual and bisexual men, intravenous drug users who share needles, hemophiliacs who have received factor VIII transfusions, and the sexual partners of all the foregoing. Neurologic complications of AIDS include dementia, myelopathy, neuropathy, myopathy, and stroke. In addition, patients with AIDS are at increased risk for developing acute confusional states resulting from direct viral involvement of the nervous system, opportunistic infections, and tumors associated with AIDS.

1. HIV-1 MENINGITIS

Patients infected with HIV-1 can develop a syndrome characterized by headache, fever, signs of meningeal irritation, cranial nerve (especially VII) palsies, other focal neurologic abnormalities, or seizures. This usually occurs at about the time of HIV-1 seroconversion. An acute confusional state is occasionally also present. HIV-1 meningitis is associated with mononuclear pleocytosis of up to about 200 cells/μL and may represent the initial immunologic response of the nervous system to HIV-1 infection. A similar CSF profile has been found in some asymptomatic patients undergoing lumbar puncture shortly after HIV-l seroconversion. Symptoms usually resolve spontaneously within about 1 month. Other causes of pleocytosis associated with AIDS, including cryptococcal meningitis, herpes simplex encephalitis, and cerebral toxoplasmosis, must be excluded; specific treatments exist for these conditions.

2. CRYPTOCOCCAL MENINGITIS

Cryptococcal meningitis occurs in 5-10% of patients with AIDS. Clinical features include headache, confusion, stiff neck, fever, nausea and vomiting, seizures, and cranial nerve palsies. Because the CSF is otherwise normal in about 20% of patients with AIDS and cryptococcal meningitis, CSF cryptococcal antigen titers should always be obtained. Laboratory abnormalities and recommended treatment are discussed in the section on fungal meningitis.

3. HERPES SIMPLEX & VARICELLA-ZOSTER ENCEPHALITIS

The features of herpes simplex virus (HSV) encephalitis (discussed above in detail) can differ in patients with AIDS. While HSV encephalitis in immunocompetent adults is almost always due to type 1 virus, either type 1 or type 2 HSV can produce the disorder in patients with AIDS. The focal neurologic signs and CSF abnormalities usually associated with HSV encephalitis may be absent in AIDS, and the disorder may follow a more indolent course. Varicella-zoster virus, a herpesvirus that rarely causes encephalitis in immunocompetent individuals, may do so in patients with AIDS. Treatment is as described above for HSV encephalitis.

4. CYTOMEGALOVIRUS ENCEPHALITIS

Cytomegalovirus, another herpesvirus, has been implicated as a cause of retinitis and polyradiculomyelitis in patients with AIDS. Cytomegalovirus can also be identified in CSF and biopsy specimens from patients with AIDS who are neurologically asymptomatic, acutely confused, or demented. In some symptomatic cases, autopsy shows microglial nodules and cytomegalovirus inclusions. Death usually occurs within a few weeks, although therapeutic responses to antiviral treatment with ganciclovir and foscarnet have been reported.

5. CEREBRAL TOXOPLASMOSIS

Cerebral toxoplasmosis produces intracerebral mass lesions in patients with AIDS, although its frequency appears to be declining as anti toxoplasma drugs such as trimethoprim-sulfamethoxazole are widely used for prophylaxis against *Pneumocystis carinii* pneumonia in patients with AIDS. A confusional state lasting days to weeks exists at the time of presentation in about 30% of patients. Other clinical features include fever, focal neurologic abnormalities such as cranial nerve palsies or hemiparesis, seizures, headache, and signs of meningeal irritation. Serologic tests for toxoplasmosis are unreliable in patients with AIDS. CT scanning typically reveals one or more lesions, which often show a contrast enhancement of the rim and are commonly located in the basal ganglia;

MRI is more sensitive than CT in revealing the lesions. Because toxoplasmosis is readily treatable, patients with AIDS and intracerebral mass lesions that are not obviously due to stroke should be treated for presumed toxoplasmosis, as described in the section on parasitic infections (below). Up to 90% of patients respond favorably to therapy within the first few weeks and the majority survive longer than 6 months.

FUNGAL MENINGITIS

In a small fraction of patients with systemic fungal infections (mycoses), fungi invade the central nervous system to produce meningitis or focal intraparenchymal lesions. Several of these fungi are opportunistic organisms that cause infection in patients with cancer, patients receiving corticosteroids or other immunosuppressive drugs, and other debilitated hosts. Intravenous drug abuse is a potential route for infection with *Candida* and *Aspergillus*. Diabetic acidosis is strongly correlated with rhinocerebral mucormycosis. In contrast, meningeal infections with *Coccidioides, Blastomyces,* and *Actinomyces* usually occur in previously healthy individuals. *Cryptococcus* (the most common cause of fungal meningitis in the United States) and *Histoplasma* infection can occur in either healthy or immunosuppressed patients. Cryptococcal meningitis is the most common fungal infection of the nervous system in AIDS, but *Coccidioides* and *Histoplasma* infections can also occur in this setting. Geographic factors are also important in the epidemiology of certain mycoses.

Pathogenesis

Organisms reach the central nervous system by hematogenous spread from the lungs, heart, gastrointestinal or genitourinary tract, or skin or by direct extension from parameningeal sites such as the orbits or paranasal sinuses. Invasion of the meninges from a contiguous focus of infection is particularly common in mucormycosis but may also occur in aspergillosis and actinomycosis.

Pathology

Pathologic findings in fungal infections of the nervous system include a primarily mononuclear meningeal exudative reaction, focal abscesses or granulomas in the brain or spinal epidural space, cerebral infarction related to vasculitis, and ventricular enlargement caused by communicating hydrocephalus.

Clinical Findings

Fungal meningitis is usually a subacute illness that clinically resembles tuberculous meningitis. A history of such predisposing conditions as carcinoma, hematologic cancer, AIDS, diabetes, organ transplantation, treatment with corti-

costeroids or cytotoxic agents, prolonged antibiotic therapy, or intravenous drug use increases the suspicion of opportunistic infection. Questions should be asked about recent travel through areas where certain fungi are endemic.

A. Symptoms and Signs. Common symptoms include headache and lethargy or confusion. Nausea, vomiting, visual loss, seizures, or focal weakness may be noted, while fever may be absent. In a diabetic patient with acidosis, complaints of facial or eye pain, nasal discharge, proptosis, or visual loss should urgently alert the physician to the likelihood of *Mucor* infection.

Careful examination of the skin, orbits, sinuses, and chest may reveal evidence of systemic fungal infection. Neurologic examination may show signs of meningeal irritation, a confusional state, papilledema, visual loss, ptosis, exophthalmos, ocular or other cranial nerve palsies, and focal neurologic abnormalities such as hemiparesis. Because some fungi (most commonly *Cryptococcus)* can cause spinal cord compression, there may be evidence of spine tenderness, paraparesis, pyramidal signs in the legs, and loss of sensation over the legs and trunk.

B. Laboratory Findings. Blood cultures should be obtained. Serum glucose and arterial blood gas levels should be determined in diabetic patients. The urine should be examined for *Candida.* Chest x-ray may show hilar lymphadenopathy, patchy or miliary infiltrates, cavitation, or pleural effusion. The CT scan or MRI may demonstrate intracerebral mass lesions associated with *Cryptococcus* or other organisms, a contiguous infectious source in the orbit or paranasal sinuses, or hydrocephalus.

CSF pressure may be normal or elevated, and the fluid is usually clear. It may be viscous in the presence of numerous cryptococci, but the presence of alcohol (once considered indicative of cryptococcal infection) is not a reliable finding. Lymphocytic pleocytosis of up to 1000 cells/μL is common, but a normal cell count or polymorphonuclear pleocytosis can be seen in early fungal meningitis and normal cell counts are common in immunosuppressed patients. *Aspergillus* infection typically produces a polymorphonuclear pleocytosis. CSF protein, which may be normal initially, subsequently rises, usually to levels not exceeding 200 mg/dL. Higher levels (<1 g/dL) suggest possible subarachnoid block. Glucose is normal or decreased but rarely below 10 mg/dL. Microscopic examination of Gram-stained and acid-fast smears and India ink preparations may reveal the infecting organism. Fungal cultures of CSF and other body fluids and tissues should be obtained, but they are often negative. In suspected mucormycosis, biopsy of the affected tissue (usually nasal mucosa) is essential. Useful CSF serologic studies include cryptococcal antigen and *Coccidioides* complement-fixing antibody. Cryptococcal antigen is more sensitive than India ink for detecting *Cryptococcus,* and should always be looked for in both CSF and serum when that organism is suspected (in patients with AIDS, for example).

Differential Diagnosis

Fungal meningitis may mimic brain abscess and other subacute or chronic meningitides, such as those due to tuberculosis or syphilis. CSF findings and contrast CT scans are useful in differential diagnosis.

Treatment & Prognosis

For most organisms causing fungal meningitis, treatment is begun with amphotericin B deoxycholate, 1 mg intravenously as a test dose given over 20-30 minutes, followed the next day by 0.3 mg/kg intravenously in 5% dextrose, given over 2-3 hours. The dose is then increased daily in 5- to 10-mg increments until a maximal dose of 0.5-1.5 mg/kg/d is reached. Treatment is usually continued for 12 weeks. Nephrotoxicity is common with amphotericin B and may force interruption of therapy for 2-5 days. Newer, lipid-based formulations (eg, amphotericin B lipid complex, amphotericin B cholesteryl sulfate, liposomal amphotericin B) are less nephrotoxic, and can be used in patients who develop such toxicity on amphotericin B deoxycholate.

In patients with *Coccidioides* meningitis or those not responding to intravenous therapy, intrathecal amphotericin B (usually administered via an Ommaya reservoir) is added. The drug is given as a 0.1-mg test dose diluted in 10 mL of CSF, with or without added corticosteroids, and increased to 0.25-0.5 mg every other day. Because administration of amphotericin into the CSF may produce side effects, may require instillation at multiple sites, and may be unsuccessful, another approach is to give fluconazole, 400-600 mg/d, or itraconazole, 200 mg twice daily with meals, by the oral route. In this case, treatment must be continued indefinitely.

In cryptococcal meningitis, flucytosine, 100 mg/kg/d orally, added to amphotericin B and given in four divided doses, reduces the duration of therapy from 12 to 6 weeks. The dose of flucytosine must be reduced in renal failure; the major side effect is bone marrow suppression, which is usually reversible. Because of this toxicity, flucytosine is usually omitted when treating cryptococcal meningitis in patients with AIDS. For patients with AIDS and cryptococcal meningitis who do not respond to amphotericin B alone, fluconazole can be added at an initial dose of 400 mg, followed by 200 mg/d, orally or intravenously, for at least 10-12 weeks after CSF cultures are negative. Long-term maintenance therapy with fluconazole, 100-200 mg/d orally, may also reduce the likelihood of recurrence following successful treatment of cryptococcal meningitis in patients with AIDS.

Rapid correction of hyperglycemia and acidosis must be combined with amphotericin B treatment and surgical debridement of necrotic tissue in diabetics with mucormycosis. Mortality rates remain high in fungal meningitis. The complications of therapy are frequent, and neurologic residua are common.

PARASITIC INFECTIONS

Protozoal and helminthic infections are important causes of central nervous system disease, particularly in immunosuppressed patients (including those with AIDS), and in certain regions of the world. Rickettsias, the parasitic bacteria that cause Rocky Mountain spotted fever, rarely affect the nervous system.

1. MALARIA

Malaria is caused by the protozoan *Plasmodium falciparum* or another *Plasmodium* species that is transferred to humans by the female *Anopheles* mosquito. Clinical features include fever, chills, myalgia, nausea and vomiting, anemia, renal failure, hypoglycemia, and pulmonary edema. Although malaria is, worldwide, the most common parasitic infection of humans, cerebral involvement is rare. Plasmodia reach the central nervous system in infected red blood cells and cause occlusion of cerebral capillaries. Neurologic involvement becomes apparent weeks after infection. In addition to acute confusional states, cerebral malaria can produce seizures and, rarely, focal neurologic abnormalities. The diagnosis is made by finding plasmodia in red blood cells of peripheral blood smears. The CSF may show increased pressure, xanthochromia, mononuclear pleocytosis, or mildly elevated protein.

Prophylaxis

Malaria prophylaxis is recommended for travelers to areas where the disease is endemic and consists of chloroquine phosphate, 500 mg orally, weekly. If exposure to chloroquine-resistant strains is expected, mefloquine (250 mg orally weekly for 4 weeks, then every other week for 4 weeks) should be given instead. Both regimens are started one week before the initial exposure and continued for 4 weeks after exposure ends.

Treatment

Chloroquine-sensitive cerebral malaria is treated with chloroquine, 10 mg base/kg by continuous intravenous infusion over 8 hours followed by 15 mg base/kg over 24 hours, or 3.5 mg base/kg by the intramuscular or subcutaneous route every 6 hours to a cumulative dose of ~25 mg base/kg. Chloroquine-resistant cerebral malaria is treated with quinidine, 10 mg base/kg by intravenous infusion over 1 hour followed by 0.02 mg base/kg/min, or with quinine dihydrochloride, 20 mg/kg by intravenous infusion over 4 hours followed by 10 mg/kg infused over 2-8 hours every 8 hours. Each of these regimens is continued until oral therapy with chloroquine, amodiaquine, or sulfadoxine and pyrimethamine (for chloroquine-sensitive malaria) or with mefloquine, quinine, or quinidine (for chloroquine-resistant malaria) can be substituted. Cerebral edema is not a consistent finding in cerebral malaria, and corticosteroids are not

helpful and may, in fact, be deleterious. The mortality rate in cerebral malaria is 20-50% and reaches 80% in cases complicated by coma and seizures.

2. TOXOPLASMOSIS

Acquired (as opposed to congenital) toxoplasmosis results from ingestion of *Toxoplasma gondii* cysts in raw meat or cat excrement and is usually asymptomatic. Symptomatic infection is associated with underlying malignant disease (especially Hodgkin's disease), immunosuppressive therapy, or AIDS. Systemic manifestations include skin rash, lymphadenopathy, myalgias, arthralgias, carditis, pneumonitis, and splenomegaly. Central nervous system involvement can take several forms.

Clinical Findings

The CSF may be normal, or it may show mild mononuclear cell pleocytosis or slight protein elevation. A CT scan may show one or more ring-enhancing lesions, especially if a double dose of contrast material is used. Lesions revealed by CT scan may fail to enhance, however, and autopsy-proved lesions may not be detected by CT. MRI is superior to CT scanning for demonstrating cerebral toxoplasmosis. The diagnosis is made by blood tests demonstrating a high ($\geq$ 1:32,000) or rising Sabin-Feldman dye test titer or IgM antibodies to *Toxoplasma* by indirect immunofluorescence techniques. Accurate diagnosis requires appropriate serologic studies in the immunosuppressed patient who develops neurologic symptoms.

Treatment

Treatment is with pyrimethamine, 25-100 mg/d orally and sulfadiazine, 1-1.5 g orally four times daily, and is continued for 3-4 weeks in immunocompetent patients and for at least several months in patients with AIDS or other immunodeficiency states. Clindamycin, 600 mg orally four times a day, may be substituted for sulfonamides in patients who develop drug sensitivity rashes. Folinic acid (leucovorin), 10 mg orally daily, is added to prevent pyrimethamine-induced leukopenia and thrombocytopenia.

3. PRIMARY AMEBIC MENINGOENCEPHALITIS

The free-living ameba *Naegleria fowleri* causes primary amebic meningoencephalitis in previously healthy young patients exposed to polluted water. Amebas gain entry to the central nervous system through the cribriform plate, producing a diffuse meningoencephalitis that affects the base of the frontal lobes and posterior fossa. It is characterized by headache, fever, nausea and vomiting, signs of meningeal irritation, and disordered mental status. Seizures and focal neurologic signs are rare. The CSF shows a polymorphonuclear pleocytosis with

elevated protein and low glucose; highly motile, refractile trophozoites can be seen on wet mounts of centrifuged CSF. The disease is usually fatal within 1 week, although treatment with amphotericin B, 1 mg/kg/d intravenously, may be effective, as may a combination of amphotericin B, rifampin, and chloramphenicol or ketoconazole.

4. GRANULOMATOUS AMEBIC ENCEPHALITIS

Granulomatous amebic encephalitis results from infection with the *Acanthamoeba/Hartmanella* species and commonly occurs in the setting of chronic illness or immunosuppression. The disorder typically lasts for periods from 1 week to 2 or 3 months and is characterized by subacute or chronic meningitis and granulomatous encephalitis. The cerebellum, brain stem, basal ganglia, and cerebral hemispheres are affected. An acute confusional state is the most common clinical finding. Although fever, headache, and meningeal signs are less common than in primary amebic meningoencephalitis (each occurring in only about half of patients), seizures and hemiparesis are more common. Cranial nerve palsies, cerebellar ataxia, and aphasia may occur. Pleocytosis may be primarily lymphocytic or polymorphonuclear; protein is elevated, and glucose is low or normal. Sluggishly motile trophozoites may be seen on wet mounts. Successful treatment has not been reported.

5. CYSTICERCOSIS

Cysticercosis is common in Mexico, Central and South America, and certain regions of Africa, Asia, and Europe. The disease follows ingestion of larvae of the pork tapeworm *(Taenia solium)* and affects the brain in 60-90% of cases. Larvae undergo hematogenous dissemination, forming cysts in the brain, ventricles, and subarachnoid space. Neurologic manifestations of cysticercosis result from the mass effect of intraparenchymal cysts, obstruction of CSF flow by intraventricular cysts, or inflammation that causes basilar meningitis. They include seizures, headache, focal neurologic signs, hydrocephalus, myelopathy, and subacute meningitis. Peripheral blood eosinophilia, soft tissue calcifications on x-ray, or the presence of parasites in the stool suggests the diagnosis. The CSF typically shows a lymphocytic pleocytosis (< 100 cells/μL), with eosinophils usually but not always present. Opening pressure is often increased but may be decreased with spinal subarachnoid block. Protein is increased to 50-100 mg/dL, and glucose is 20-50 mg/dL in most cases. Complement fixation and hemagglutination studies can assist in the diagnosis. The CT scan may show contrast-enhanced mass lesions with surrounding edema, intracerebral calcifications, or ventricular enlargement. Myelography should be performed in suspected spinal subarachnoid block.

The indications for treatment of cerebral cysticercosis are controversial. However, patients with symptomatic neurologic involvement (usually seizures) and either meningitis or one or more noncalcified intraparenchymal cysts should be treated. Intraventricular, subarachnoid, and racemose cysts respond poorly to treatment, and calcified cysts do not require treatment. Albendazole, 15 mg/kg/d in three doses taken with meals, and continued for 8 days, is the preferred therapy. Praziquantel, 50 mg/kg/d in three divided doses, can also be used, but blood levels are reduced by anticonvulsants and corticosteroids, which are often also required in these patients. Patients with seizures should also receive anticonvulsants. Corticosteroids are indicated for increased intracranial pressure or lesions near the cerebral aqueduct or intraventricular foramina; these may progress to cause obstructive hydrocephalus. Single accessible intraparenchymal lesions can be removed surgically, and shunting is required for intraventricular lesions causing hydrocephalus.

6. ANGIOSTRONGYLUS CANTONENSIS MENINGITIS

Angiostrongylus cantonensis is endemic to Southeast Asia and to Hawaii and other Pacific islands. Infection is transmitted by ingestion of infected raw mollusks and produces meningitis with CSF eosinophilia. Most patients complain of headache, and about half report stiff neck, vomiting, fever, and paresthesias. Most patients have a CSF leukocytosis of 150-1500/μL, mild elevation of protein, and normal glucose. The acute illness usually resolves spontaneously in 1-2 weeks, although paresthesias may persist longer. Levamisole, albendazole, thiabendazole, mebendazole, and ivermectin have been used for treatment, and mebendazole 100 mg twice daily orally for 5 days may be preferred. Analgesics, corticosteroids, and reduction of CSF pressure by repeated lumbar punctures may be of value.

7. ROCKY MOUNTAIN SPOTTED FEVER

Rocky Mountain spotted fever is caused by *Rickettsia rickettsii,* an intracellular parasite transmitted to humans by tick bites. *R rickettsii* damages endothelial cells, leading to vasculitis, microinfarcts, and petechial hemorrhage. Initial symptoms include fever, headache, and a characteristic rash that involves the palms and soles and spreads centrally. Neurologic involvement, which is uncommon, produces a confusional state and, less often, coma or focal neurologic abnormalities. The CSF is normal or shows a mild mononuclear pleocytosis. Treatment is with chloramphenicol, 25-50 mg/kg/d orally or intravenously in four divided doses, or doxycycline, 200 mg/d orally or intravenously, and is continued for 7 days. Neurologic residua may occur.

PERIPHERAL NERVE LESIONS

Classification

A. Mononeuropathy Simplex. This term signifies involvement of a single peripheral nerve.

B. Mononeuropathy Multiplex. In this disorder, several individual nerves are affected, usually at random and noncontiguously. Clinical examination reveals a clinical deficit attributable to involvement of one or more isolated peripheral nerves, except when mononeuropathy multiplex is extensive and the resulting deficits become confluent.

Causes of peripheral neuropathy

Idiopathic inflammatory neuropathies
- Acute idiopathic polyneuropathy (Guillain-Barre syndrome)
- Chronic inflammatory demyelinating polyneuropathy

Metabolic and nutritional neuropathies
- Diabetes
- Other endocrinopathies
  - Hypothyroidism
  - Acromegaly
- Uremia
- Liver disease
- Vitamin B_{12} deficiency

Infective and granulomatous neuropathies
- AIDS
- Leprosy
- Diphtheria
- Sarcoidosis
- Sepsis and multiorgan failure

Vasculitic neuropathies
- Polyarteritis nodosa
- Rheumatoid arthritis
- Systemic lupus erythematosus

Neoplastic and paraproteinemic neuropathies
- Compression and infiltration by tumor
- Paraneoplastic syndromes
- Paraproteinemias
- Amyloidosis

Drug-induced and toxic neuropathies
- Alcohol
- Other drugs
  - Dapsone
  - Hydralazine
  - Isoniazid
  - Phenytoin
  - Pyridoxine
  - Vincristine
- Toxins
  - Organic compounds
    - Hexacarbons
    - Organophosphates
- Heavy metals
  - Arsenic
  - Lead
  - Thallium
  - Gold
  - Platinum
- Tryptophan (contaminant)

Hereditary neuropathies
- Idiopathic
  - Hereditary motor and sensory neuropathies
  - Hereditary sensory neuropathies
  - Friedreich's ataxia
  - Familial amyloidosis
- Metabolic
  - Porphyria
  - Metachromatic leukodystrophy
  - Krabbe's disease
  - Abetalipoproteinemia
  - Tangier's disease
  - Refsum's disease
  - Fabry's disease

Entrapment neuropathies

C. Polyneuropathy. This term denotes a disorder in which the function of numerous peripheral nerves is affected at the same time. This leads to a predominantly distal and symmetric deficit with loss of tendon reflexes. Polyneuropathies are sometimes subclassified according to the primary site at which the nerve is affected. In **distal axonopathies**, the axon is the principal pathologic target; most polyneuropathies fall into this category. **Myelinopathies** are conditions that involve the myelin sheath surrounding the axon. These disorders in-

clude acute idiopathic polyneuropathy (Guillain-Barre syndrome), chronic inflammatory demyelinating neuropathy, diphtheria, certain paraneoplastic and paraproteinemic states, and some hereditary metabolic conditions (metachromatic leukodystrophy, type III hereditary motor and sensory neuropathy, Krabbe's disease). Finally, certain disorders – termed **neuronopathies** – principally affect nerve cell bodies in the anterior horn of the spinal cord or dorsal root ganglion. Examples are type 11 hereditary motor and sensory neuropathy, pyridoxine-induced neuropathy, and some paraneoplastic syndromes.

Clinical Findings

A. Sensory Disturbances. Involvement of sensory fibers can lead to numbness and impaired sensation. It can also lead to abnormal spontaneous sensations, such as pain and paresthesias, and to perverted sensations such as hyperpathia.

1. Pain is a conspicuous feature of certain neuropathies, especially if small fibers within the nerves are affected. The precise mechanism of its genesis is unclear. Polyneuropathies associated with prominent pain include those related to diabetes, alcoholism, porphyria, Fabry's disease, amyloidosis, rheumatoid arthritis, and AIDS, as well as dominantly inherited sensory neuropathy and paraneoplastic sensory neuronopathy. Pain is also a feature of many entrapment neuropathies and of idiopathic brachial plexopathy.

2. Dissociated sensory loss is impairment of some sensory modalities, such as pain and temperature, with preservation of others, such as light touch, vibration, and joint position sense. Although the presence of a dissociated sensory loss often indicates a spinal cord lesion, it also occurs in peripheral neuropathies when there is selective involvement of peripheral nerve fibers of a certain size, such as occurs in amyloid neuropathy, leprous neuritis, or hereditary sensory neuropathy. In such cases, preferential involvement of small fibers is commonly associated with disproportionate impairment of pain and temperature appreciation, spontaneous pain, and autonomic dysfunction. Large-fiber disease, on the other hand, results in defective touch, vibration, and joint position sense, early loss of tendon reflexes, and prominent motor symptoms.

B. Motor Deficits. The motor deficit that occurs with a peripheral nerve lesion consists of weakness of muscles innervated by the nerve, accompanied in severe cases by wasting and fasciculation. There may be difficulty in the performance of fine tasks; this is compounded by any accompanying sensory loss. The clinical findings reflect a lower motor neuron deficit, and it is the distribution of these signs and the presence of accompanying sensory and reflex changes that suggest they may be due to peripheral nerve involvement.

C. Tendon Reflexes. These are impaired or lost if reflex arcs are interrupted on either the afferent or efferent side (C5-6, biceps and brachioradialis;

C7-8, triceps; L3-4, knee; SI, ankle). The ankle jerks are usually the first to be lost in patients with polyneuropathies.

D. Autonomic Disturbances. Autonomic disturbances may be particularly conspicuous in some peripheral neuropathies – especially Guillain-Barre syndrome and neuropathies related to diabetes, renal failure, porphyria, or amyloidosis. Symptoms include postural hypotension, coldness of the extremities, impaired thermoregulatory sweating, disturbances of bladder and bowel function, and impotence.

E. Enlarged Nerves. Palpably enlarged peripheral nerves raise the possibility of leprosy, amyloidosis, hereditary motor and sensory neuropathies, Refsum's disease, acromegaly, or chronic inflammatory demyelinating polyneuropathy.

Evaluation of Patients

A. Time Course. Polyneuropathy that develops acutely over a few days usually relates to an inflammatory process, as in the Guillain-Barre syndrome. It may also relate to an underlying neoplasm, to infections such as diphtheria, to metabolic disorders such as acute intermittent porphyria, or to exposure to such toxic substances as thallium or triorthocresyl phosphate. A chronic course with a gradual evolution over several years is typical of many hereditary or metabolic polyneuropathies but also characterizes chronic inflammatory demyelinating polyneuropathy.

Mononeuropathy of acute onset is likely to be traumatic or ischemic in origin, while one evolving gradually is more likely to relate to entrapment (ie, compression by neighboring anatomic structures) or to recurrent minor trauma.

B. Age at Onset. Polyneuropathies that develop during childhood or early adult life often have a hereditary basis, but they may also relate to an underlying inflammatory disorder. Those developing in later life are more likely to be due to a metabolic, toxic, or inflammatory disorder or to an underlying neoplasm.

Mononeuropathy presenting in the neonatal period is likely to be developmental in origin or related to birth injury; one developing in later life may relate to entrapment or injury that is often occupationally determined.

C. Occupational History. Various industrial substances can lead to peripheral neuropathy, including carbon disulfide, n-hexane, ethylene oxide, methyl bromide, acrylamide, triorthocresyl phosphate and certain other organophosphates, DDT, arsenic, lead, and thallium. A mononeuropathy is sometimes the first clinical manifestation of an occupationally related polyneuropathy, but it may also develop in response to entrapment or recurrent minor occupational trauma. For example, carpal tunnel syndrome is more common in persons who do heavy manual labor or develop repetitive motion injury as a result of computer terminal use, and a lesion of the deep palmar branch of the ulnar nerve may relate to repeated pressure on the palm of the hand by, for example, punch-

ing down heavily on a stapler or using heavy equipment such as a pneumatic road drill.

D. Medical History:

1. Peripheral neuropathy may relate to **metabolic disorders** such as diabetes mellitus, uremia, liver disease, myxedema, acromegaly, metachromatic leukodystrophy, or Fabry's disease. That caused by diabetes is especially important and may take the form of an entrapment mono neuropathy, acute ischemic mononeuritis, distal sensorimotor polyneuropathy, subacute proximal motor polyradiculopathy (diabetic amyotrophy), thoracoabdominal radiculopathy, or autonomic neuropathy.

2. A peripheral neuropathy may also relate to an underlying malignant **neoplasm**. The peripheral nerves, spinal nerves, and limb plexuses may be compressed or infiltrated by extension of primary tumors or metastatic lymph nodes. Neoplastic disease can also lead to a nonmetastatic (paraneoplastic) sensory or sensorimotor polyneuropathy or to Lambert-Eaton syndrome.

3. Certain **connective tissue disorders**, especially polyarteritis nodosa, rheumatoid arthritis, Churg-Strauss syndrome, and Wegener's granulomatosis, may be associated with mononeuropathy multiplex or, less commonly, polyneuropathy or cranial neuropathy. Polyneuropathy is more common in systemic lupus erythematosus. Patients with rheumatoid arthritis are particularly likely to develop focal entrapment or compressive mononeuropathies in the vicinity of the affected joints.

4. AIDS is commonly associated with a distal, symmetric, primarily sensory polyneuropathy. Peripheral nerve involvement in AIDS less frequently takes the form of an acute or chronic inflammatory demyelinating polyneuropathy, polyradiculopathy, mononeuropathy multiplex, or autonomic neuropathy. Neuropathies are also seen in patients with AIDS-related complex, asymptomatic human immunodeficiency virus-1 (HIV-1) infection, and HIV-1 seroconversion.

E. Drug and Alcohol History. Some of the drugs that cause peripheral neuropathy are shown in table; there may be selective involvement of motor or sensory fibers with some drugs:

Sensory neuropathy
- Chloramphenicol
- Cisplatin
- Pyridoxine
- Taxotere

Predominantly sensory neuropathy
- Ethambutol
- Hydralazine
- Misonidazole
- Metronidazole

Motor neuropathy

Dapsone
Imipramine
Certain sulfonamides

Mixed sensory and motor neuropathy

Amiodarone
Chloroquine
Disulfiram
Gold
Indomethacin
Isoniazid
Nitrofurantoin
Penicillamine
Perhexilene
Phenytoin
Thalidomide
Tryptophan (contaminant)
Vincristine

F. Family Background. Certain polyneuropathies have a hereditary basis. These are discussed later in this chapter in the section on hereditary neuropathies.

Differential Diagnosis

Peripheral neuropathies can lead to a motor or sensory deficit or both. The preservation of sensation and tendon reflexes distinguishes the motor deficit that results from pure pyramidal lesions or is associated with spinal muscular atrophies, myopathies, or disorders of neuromuscular transmission from that caused by peripheral nerve involvement.

Myelopathies are characterized by a pyramidal deficit below the level of the lesion as well as by distal sensory loss.

In tabes dorsalis, there is often a history of syphilitic infection, and examination reveals other stigmas of syphilis. In addition, tactile sensation is preserved.

Radiculopathies are distinguished from peripheral neuropathies by the distribution of motor or sensory deficits. The presence of neck or back pain that radiates to the extremities in a radicular distribution also suggests a root lesion.

Investigative Studies

Laboratory studies in patients with peripheral neuropathy are directed at confirming the diagnosis and revealing any underlying cause. Electromyography may reveal evidence of denervation in the affected muscles and can be used to determine whether any motor units remain under voluntary control. Nerve con-

duction studies permit conduction velocity to be measured in motor and sensory fibers. On the basis of electrodiagnostic or histopathologic studies, peripheral neuropathies can be divided into demyelinating or axonal neuropathies. In the former, electromyography typically reveals little or no evidence of denervation but there is conduction block or marked slowing of maximal conduction velocity in affected nerves. In the axonal neuropathies, electromyography shows that denervation has occurred, especially distally in the extremities, but maximal nerve conduction velocity is normal or slowed only slightly.

In patients with electrophysiologically confirmed peripheral neuropathy, laboratory studies should include a complete blood count; erythrocyte sedimentation rate; serum urea nitrogen and creatinine, fasting blood glucose, and serum vitamin B_{12}; serum protein, protein electrophoresis, and immunoelectrophoresis; liver and thyroid function blood tests; serologic tests for syphilis (FTA or MHA-TP), rheumatoid factor, and antinuclear antibody; and chest x-ray. If toxic causes are suspected, a 24-hour urine collection followed by analysis for heavy metals may be necessary, and hair and fingernail clippings can be analyzed for arsenic. Examination of a fresh specimen of urine for porphobilinogen and δ-aminolevulinic acid is necessary if porphyria is suspected.

Treatment

Treatment of the underlying cause may limit the progression of or even reverse the neuropathy. Nursing care is important in patients with severe motor or sensory deficits to prevent decubitus ulcers, joint contractures, and additional compressive peripheral nerve damage. Respiratory function must also be monitored carefully-particularly in acute idiopathic polyneuropathy (Guillain-Barre syndrome), chronic inflammatory demyelinating polyneuropathy, and diphtheritic neuropathy-and preparations must be made to assist ventilation if the vital capacity falls below about 1 L. In patients with severe dysesthesia, a cradle (inverted metal bar frame) can be used to keep the bedclothes from touching sensitive areas of the skin. Treatment with phenytoin, 300 mg/d; carbamazepine, up to 1200 mg/d; or mexiletine, 600-900 mg/d is sometimes helpful in relieving the lancinating pain of certain neuropathies. If the pain is more constant, burning, or dysesthetic, amitriptyline 25-100 mg at bedtime is often helpful. Gabapentin (300 mg three times daily) has not been definitively evaluated but many patients report symptom amelioration with it when the first-line drugs are not tolerated.

Extremities with sensory loss must be protected from repeated minor trauma, such as thermal injury, that can destroy tissues. The temperature of hot surfaces should be checked with a part of the body in which sensation is preserved, and the setting of water heaters must be reduced to prevent scalding. The skin and nails must be cared for meticulously.

Dysautonomic symptoms may be troublesome, especially in diabetic or alcoholic polyneuropathy. Waist-high elastic hosiery, dietary salt supplementa-

tion, and treatment with fludrocortisone, 0.1-1 mg/d orally, may help relieve postural hypotension, but the patient must be monitored carefully to prevent recumbent hypertension. Instructing the patient to sleep in a semierect rather than a recumbent position is helpful because dysautonomic patients are often unable to conserve salt and water when recumbent at night.

POLYNEUROPATHIES

IDIOPATHIC INFLAMMATORY NEUROPATHIES

Acute Idiopathic Polyneuropathy (Guillain-Barre Syndrome)

Guillain-Barre syndrome is an acute or subacute polyneuropathy that can follow minor infective illnesses, inoculations, or surgical procedures-or may occur without obvious precipitants. Clinical and epidemiologic evidence suggests an association with preceding *Campylobacter jejuni* infection. Its precise cause is unclear, but it appears to have an immunologic basis. Both demyelinating and axonal forms have been recognized, with distinctive clinical and electrophysiologic features. The demyelinative form is more common in the United States, but an axonal variant is encountered occasionally (acute motor sensory axopal neuropathy). In northern China a related axonal form occurs frequently and has been designated acute motor axonal neuropathy.

A. Clinical Features. The features useful for diagnosing Guillain-Barre syndrome are summarized below. Patients generally present with weakness that is symmetric, usually begins in the legs, is often more marked proximally than distally, and is sometimes so severe that it is life-threatening, especially if the muscles of respiration or swallowing are involved. Muscle wasting develops if axonal degeneration has occurred. Sensory complaints, while usually less marked than motor symptoms, are also frequent. The deep tendon reflexes are typically absent. There may be marked autonomic dysfunction, with tachycardia, cardiac irregularities, labile blood pressure, disturbed sweating, impaired pulmonary function, sphincter disturbances, paralytic ileus, and other abnormalities.

Diagnostic criteria for Guillain-Barre syndrome:

Required for diagnosis

Progressive weakness of more than one limb
Distal areflexia with proximal areflexia or hyporeflexia

Supportive of diagnosis

Progression for up to 4 weeks
Relatively symmetric deficits

Mild sensory involvement
Cranial nerve (especially VII) involvement
Recovery beginning within 4 weeks after progression stops
Autonomic dysfunction
No fever at onset
Increased CSF protein after 1 week
CSF white blood cell count $\leq 10/\mu l$
Nerve conduction slowing or block by several weeks

Against diagnosis

Markedly asymmetric weakness
Bowel or bladder dysfunction (at onset or persistent)
CSF white blood cell count >50 or PMN count $>0/\mu l$
Well-demarcated sensory level

Excluding diagnosis

Isolated sensory involvement
Another polyneuropathy that explains clinical picture

B. Investigative Studies. The CSF often shows a characteristic abnormality, with increased protein concentration but a normal cell count; abnormalities may not be found in the first week, however. Electrophysiologic studies may reveal marked slowing of motor and sensory conduction velocity, or evidence of denervation and axonal loss. The time course of the electrophysiologic changes does not necessarily parallel any clinical developments.

C. Treatment. Plasmapheresis appears to reduce the time required for recovery and may decrease the likelihood of residual neurologic deficits. It is best instituted early, and it is indicated especially in patients with a severe or rapidly progressive deficit or respiratory compromise. Intravenous immunoglobulin (400 mg/kg/d for 5 days) appears to be equally effective and should be used in preference to plasmapheresis in adults with cardiovascular instability and in children; the two therapies are not additive.

In the past, corticosteroids were often prescribed for patients with a progressive downhill course, but recent studies have shown that these agents may affect the outcome adversely and even increase the time necessary for recovery. Therapy is otherwise symptomatic, the aim being to prevent such complications as respiratory failure or vascular collapse. For this reason, patients who are severely affected are best managed in intensive care units, where facilities are available for monitoring and assisted respiration if necessary (eg, if the vital capacity falls below about 1 L, the patient is short of breath, or the blood oxygen saturation declines). Volume replacement or treatment with pressor agents is sometimes required to counter hypotension, and low-dose heparin may help to prevent pulmonary embolism.

D. Prognosis. Symptoms and signs cease to progress by about 4 weeks into the illness. The disorder is self-limiting, and improvement occurs over the

weeks or months following onset. About 70-75% of patients recover completely, 25% are left with mild neurologic deficits, and 5% die, usually as a result of respiratory failure. The prognosis is poorer when there is evidence of preceding Campylobacter jejuni infection, and a more protracted course and less complete recovery are also likely when axonal degeneration rather than demyelination is the primary pathology. Advanced age, the need for ventilatory support, or more rapid onset of symptoms may also predict a poorer prognosis.

Chronic Inflammatory Demyelinating Polyneuropathy

Chronic inflammatory demyelinating polyneuropathy is clinically similar to Guillain-Barre syndrome except that it follows a chronic progressive course – or a course characterized by relapses – and no improvement is apparent within the 6 months after onset. Its cause is not known. Examination of the CSF reveals findings resembling those in Guillain-Barre syndrome. The electrophysiologic findings indicate a demyelinative neuropathy with superimposed axonal degeneration.

Clinical features:

Hyporeflexia or areflexia
Weakness
- Distal upper extremity
- Dista llower extremity
- Proximal upper extremity
- Proximal lower extremity
- Respiratory muscles
- Neck
- Face

Sensory deficit on examination
- Distal lower extremity
- Distal upper extremity

Paresthesia
- Upper extremity
- Lower extremity
- Face

Pain
- Lower extremity
- Upper extremity

Dysarthria
Dysphagia
Impotence
Incontinence

The disorder is often responsive to treatment with corticosteroids (prednisone, 60-100 mg/d for 2-4 weeks, then gradually tapered to 5-20 mg every other day), which may have to be continued on a long-term basis. In nonresponsive patients, treatment with azathioprine or cyclophosphamide may be helpful. In other instances, plasmapheresis or intravenous immunoglobulin therapy (400 mg/kg/d) is beneficial, although the response is usually short-lived; treatment therefore has to be continued intermittently to maintain benefit.

METABOLIC & NUTRITIONAL NEUROPATHIES

Diabetes Mellitus

Peripheral nerve involvement in diabetes is common and may be characterized by polyneuropathy, which is of mixed (sensory, motor, and autonomic;) character in about 70% of cases and predominantly sensory in about 30%; mononeuropathy multiplex; or mononeuropathy simplex. Such clinical manifestations can occur in isolation or in any combination. The incidence of peripheral nerve involvement may be influenced by the adequacy of diabetes control, which should, in any event, be optimal.

A. Clinical Features. The most common manifestation is a distal sensory or mixed polyneuropathy, which is sometimes diagnosed, before it becomes symptomatic, from the presence of depressed tendon reflexes and impaired appreciation of vibration in the legs. Symptoms are generally more common in the legs than in the arms and consist of numbness, pain, or paresthesias. In severe cases, there is distal sensory loss in all limbs and some accompanying motor disturbance. Diabetic dysautonomia leads to many symptoms, including postural hypotension, disturbances of cardiac rhythm, impaired thermoregulatory sweating, and disturbances of bladder, bowel, gastric, and sexual function. Diabetic mononeuropathy multiplex is usually characterized by pain and weakness and often has a vascular basis. The clinical deficit will depend on the nerves that are affected. Diabetic amyotrophy is due to radiculoplexopathy, polyradiculopathy, or polyradiculoneuropathy. Pain, weakness, and atrophy of pelvic girdle and thigh muscles are typical, with absent quadriceps reflexes and little sensory loss. Diabetic mononeuropathy simplex is typically abrupt in onset and often painful. CSF protein is typically increased in diabetic polyneuropathy and mononeuropathy multiplex.

B. Treatment and Prognosis. No specific treatment exists for the peripheral nerve complications of diabetes except when the patient has an entrapment neuropathy and may benefit from a decompressive procedure. Phenytoin (200-400 mg/d orally), mexiletine (600-900 mg/d), or carbamazepine (100-600 mg orally twice daily) may help to relieve shooting or stabbing neuropathic pain, while amitriptyline (75-150 mg orally at bedtime) or a combination of ami-

triptyline and fluphenazine may be useful for treating deep, constant, aching pain.

Postural hypotension may respond to treatment with salt supplementation; sleeping in an upright position; wearing waist-high elastic hosiery; fludrocortisone, 0.1-1 mg/d; and midodrine (an α-agonist), 10 mg three times daily. Treatment is otherwise symptomatic. Diabetic amyotrophy and mononeuropathy simplex usually improve or resolve spontaneously.

Other Endocrinopathies

Hypothyroidism is a rare cause of polyneuropathy. More commonly, hypothyroidism is associated with entrapment neuropathy, especially carpal tunnel syndrome. Polyneuropathy may be mistakenly diagnosed in patients with proximal limb weakness caused by hypothyroid myopathy or in patients with delayed relaxation of tendon reflexes, a classic manifestation of hypothyroidism that is independent of neuropathy. Other neurologic manifestations of hypothyroidism such as acute confusional state, dementia, and cerebellar degeneration are discussed elsewhere.

Acromegaly also frequently produces carpal tunnel syndrome and, less often, polyneuropathy. Since many acromegalic patients are also diabetic, it may be difficult to determine which disorder is primarily responsible for polyneuropathy in a given patient.

Uremia

A symmetric sensorimotor polyneuropathy, predominantly axonal in type, may occur in uremia. It tends to affect the legs more than the arms and is more marked distally than proximally. Restless legs, muscle cramps, and burning feet have been associated with it. The extent of any disturbance in peripheral nerve function appears to relate to the severity of impaired renal function. The neuropathy itself may improve markedly with renal transplantation. Carpal tunnel syndrome (see below) has also been described in patients with renal disease and may develop distal to the arteriovenous fistulas placed in the forearm for access during hemodialysis. In patients on chronic hemodialysis, it often relates to amyloidosis and the accumulation of β_2-microglobulin.

Liver Disease

Primary biliary cirrhosis may lead to a sensory neuropathy that is probably of the axonal type. A predominantly demyelinative polyneuropathy can occur in patients with chronic liver disease. There does not appear to be any correlation between the neurologic findings and the severity of the hepatic dysfunction.

Vitamin B_{12} Deficiency

Vitamin B_{12} deficiency is associated with many features that are charac-

teristic of polyneuropathy, including symmetric distal sensory and motor impairment and loss of tendon reflexes. Because controversy exists about the relative importance of polyneuropathy and myelopathy in producing this syndrome, however, vitamin B_{12} deficiency is considered in more detail below in the section on myelopathies.

INFECTIVE & GRANULOMATOUS NEUROPATHIES

AIDS

Neuropathy is a common complication of HIV-1 infection; involvement of peripheral nerves is seen at autopsy in about 40% of patients with AIDS.

Distal symmetric **sensorimotor polyneuropathy** is the most common neuropathy associated with HIV-1 infection. Axons, rather than myelin, are primarily affected. The cause is unknown, but in some patients vitamin B_{12} deficiency or exposure to neurotoxic drugs may be responsible in part. HIV-1 is rarely identified in the affected nerves. Sensory symptoms predominate and include pain and paresthesias that affect the feet especially. Weakness is a minor or late feature. Ankle and sometimes knee reflexes are absent. The course is typically progressive and no treatment is available, but pain may be controlled pharmacologically, as described above for diabetic neuropathy. Plasmapheresis is of no benefit.

Inflammatory demyelinating polyneuropathy may occur early in HIV-1 infection and may follow an acute or chronic course. The neuropathy may be immune-mediated, but sometimes results from direct, secondary viral infection, as from cytomegalovirus. It is characterized by proximal, and sometimes distal, weakness with less-pronounced sensory disturbances and areflexia or hyporeflexia. The CSF is abnormal, with an elevated protein concentration and often a lymphocytic pleocytosis (unlike the findings in Guillain-Barre syndrome or chronic inflammatory demyelinating polyneuropathy in patients without HIV-1 infection). Some patients improve spontaneously or stabilize, and others may respond to corticosteroids, plasmapheresis, or intravenous immunoglobulins.

Lumbosacral polyradiculopathy occurs late in the course of HIV-1 infection, usually in patients with prior opportunistic infections. Cytomegalovirus infection is thought to be the cause, at least in some instances. Clinical features usually develop over several weeks and include diffuse, progressive leg weakness, back pain, painful paresthesias of the feet and perineum, lower extremity areflexia, and early urinary retention. The course may be fulminant, with ascending paralysis leading to respiratory failure. The course is more benign in some patients, however, especially when the etiology is unclear. CSF findings

include mononuclear or polymorphonuclear pleocytosis, elevated protein, and decreased glucose. It is always important to exclude meningeal lymphomatosis, cord compression, or syphilis as the underlying cause, as these require specific treatment and affect the prognosis. Patients with cytomegalovirus infection may respond to ganciclovir, 2.5 mg/kg intravenously every 8 hours for 10 days, then 7.5 mg/kg/d 5 days per week.

Mononeuropathy multiplex affects multiple cranial and peripheral nerves, resulting in focal weakness and sensory loss. Some cases may have an autoimmune basis, whereas others result from neoplastic or infectious causes (eg, cytomegalovirus infection) or from vasculopathy. In early HIV-1 infection, mononeuropathy multiplex may be a self-limited disorder restricted to a single limb, with spontaneous stabilization or improvement. Late in AIDS, multiple limbs may be affected in a progressive fashion.

Mononeuropathy simplex tends to occur acutely in early HIV-1 infection and improve spontaneously. A vascular cause is probable.

Autonomic neuropathy tends to occur late in the course of HIV-1 infections and may lead to syncopal episodes, orthostatic hypotension, disturbances of sphincter or sexual function, impaired thermoregulatory sweating, and diarrhea. The dysautonomia may relate to central or peripheral pathology. Treatment is symptomatic (as discussed earlier under diabetic neuropathy).

Diphtheria

Corynebacterium diphtheriae infects tissues of the upper respiratory tract and produces a toxin that causes demyelination of peripheral nerves. Within about I month after infection, patients may develop a cranial motor neuropathy with prominent impairment of ocular accommodation. Blurred vision is the usual presenting complaint. Extraocular muscles and the face, palate, pharynx, and diaphragm may also be affected, but the pupillary light reflex is preserved. Recovery typically occurs after several weeks. A more delayed syndrome that commonly has its onset 2-3 months following the primary infection takes the form of a symmetric distal sensorimotor polyneuropathy. Most patients recover completely.

Sarcoidosis

Sarcoidosis can produce mononeuropathy or, rarely, polyneuropathy. The mononeuropathy commonly involves cranial nerves, especially the facial nerve, in which case the resulting syndrome may be indistinguishable from idiopathic facial paralysis (Bell's palsy). X-rays of the lungs and bones and determination of serum levels of angiotensin-converting enzyme are helpful in establishing the diagnosis. Treatment with prednisone, 60 mgld orally followed by tapering doses, may speed recovery.

NEUROPATHIES IN VASCULITIS & COLLAGEN VASCULAR DISEASE

Systemic vasculitides and collagen vascular diseases can produce polyneuropathy, mononeuropathy simplex, mononeuropathy multiplex, or entrapment neuropathy.

Systemic necrotizing vasculitis includes polyarteritis nodosa and allergic angiitis and granulomatosis (Churg-Strauss syndrome). Neuropathy occurs in about 50% of patients, most often as mononeuropathy multiplex, which may manifest itself with the acute onset of pain in one or more cranial or peripheral nerves. Distal symmetric sensorimotor polyneuropathy is less common. Treatment should begin as soon as the diagnosis is made; it includes prednisone, 60-100 mg/d orally, and cyclophosphamide, 2-3 mg/d orally. Plasmapheresis may also be helpful.

Wegener's granulomatosis is associated with mononeuropathy multiplex or polyneuropathy in up to 30% of cases. Treatment is the same as for systemic necrotizing vasculitis.

Giant cell arteritis. Mononeuropathy affecting cranial nerves innervating the extraocular muscles can occur.

Rheumatoid arthritis produces entrapment neuropathy (most commonly involving the median nerve) in about 45% of patients and distal symmetric sensorimotor polyneuropathy in about 30%. Mononeuropathy multiplex is a frequent feature in cases complicated by necrotizing vasculitis.

Systemic lupus erythematosus. Neuropathy occurs in up to 20% of patients. The most common pattern is a distal, symmetric sensorimotor polyneuropathy. An ascending, predominantly motor polyneuropathy (Guillain-Barre syndrome, see above) can also occur, as may mononeuropathy simplex or multiplex, which often affects the ulnar, radial, sciatic, or peroneal nerve.

Sjogren's syndrome involves the peripheral nerves in about 20% of cases. Distal symmetric sensorimotor polyneuropathy is most common, entrapment neuropathy (affecting especially the median nerve) is also frequent, and mononeuropathy multiplex can occur.

Progressive systemic sclerosis (scleroderma) and mixed connective tissue disease may produce cranial mononeuropathy, which most often involves the trigeminal (V) nerve.

NEOPLASTIC & PARAPROTEINEMIC NEUROPATHIES

Compression & Infiltration by Tumor

Nerve compression is a common complication of multiple myeloma, lymphoma, and carcinoma. Tumorous invasion of the epineurium may occur with leukemia, lymphoma, and carcinoma of the breast or pancreas.

Paraneoplastic Syndromes

Carcinoma (especially oat-cell carcinoma of the lung) and lymphoma may be associated with neuropathies that are thought to be immunologically mediated, based on the detection of autoantibodies to neuronal antigens in several cases.

Sensory or sensorimotor polyneuropathy occurs with both carcinoma and lymphoma. This can be either an acute or chronic disorder; it is sometimes asymmetric and may be accompanied by prominent pain.

Carcinoma can also cause **sensory neuronopathy**, a polyneuropathy that primarily affects the cell bodies of sensory neurons in the dorsal root ganglion. This rare condition may be the presenting manifestation of cancer. Initial symptoms of pain and numbness usually begin distally but sometimes begin proximally or in the face. The disorders often progress over days or several weeks, leading to marked sensory ataxia and impairment of all sensory modalities. Motor involvement is late, and autonomic dysfunction is uncommon. The CSF may have an inflammatory formulation. Treatment, even of the underlying tumor, is usually unrewarding.

Lymphoma may be complicated by **motor neuronopathy**, a disorder of anterior horn cells. Hodgkin's disease and angioimmunoblastic lymphadenopathy are sometimes associated with Guillain-Barre syndrome.

Paraproteinemias

Polyneuropathy is a common complication of **multiple myeloma**. Patients affected by lytic myeloma are usually men. The clinical picture is of a distal symmetric sensorimotor polyneuropathy. All sensory modalities are affected, pain is a frequent feature, and the reflexes are depressed. The disorder is usually progressive and leads to death within 2 years. **Sclerotic myeloma** may be accompanied by a chronic demyelinating polyneuropathy. Motor involvement predominates, but vibration and position sense may also be impaired, and the reflexes are depressed. Pain is less common than in the neuropathy of lytic myeloma, and symptoms may improve with treatment of the underlying cancer or by plasmapheresis. The **POEMS syndrome** (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) may complicate plasma cell dyscrasias, especially osteosclerotic myeloma. The sensorimotor polyneuropathy may respond to treatment with corticosteroids or cyclophosphamide; irradiation of solitary osteosclerotic lesions may also be worthwhile.

A sensorimotor polyneuropathy similar to that observed with lytic myeloma may also occur in **Waldenstrom's macroglobulinemia or benign monoclonal gammopathy**. Treatment with immunosuppressant drugs and plasmapheresis is sometimes helpful.

Amyloidosis

Nonhereditary amyloidosis occurs as an isolated disorder (primary gener-

alized amyloidosis) or in patients with multiple myeloma and may be associated with polyneuropathy. Polyneuropathy is also a feature of hereditary amyloidosis. Amyloid neuropathies are considered below in the section on hereditary neuropathies.

DRUG-INDUCED & TOXIC NEUROPATHIES

Alcohol

Polyneuropathy is one of the most common neurologic complications of chronic alcoholism; it can occur alone or in combination with other alcohol-related neurologic disorders, such as Wernicke's encephalopathy or the Korsakoff amnestic syndrome. Controversy exists concerning the relative contributions of direct neurotoxicity of alcohol and associated nutritional (especially thiamine) deficiency in producing polyneuropathy.

Alcoholic polyneuropathy is typically a symmetric distal sensorimotor neuropathy. The legs are particularly likely to be affected, resulting in defective perception of vibration and touch and depressed or absent ankle reflexes. In some cases, distal weakness is also pronounced and autonomic dysfunction may occur. When pain is a prominent feature, it may respond to the same treatment described above for painful diabetic neuropathy. Abstinence from alcohol and thiamine repletion can halt the progression of symptoms.

Other Drugs

A large number of drugs have been reported to cause neuropathies.

Hydralazine, an antihypertensive drug, is associated on rare occasions with a predominantly sensory polyneuropathy that has been attributed to drug-induced pyridoxine deficiency and that resolves after the drug is discontinued.

Isoniazid is a widely used antituberculous agent that interferes with pyridoxine metabolism and produces a polyneuropathy that principally affects the sensory neurons. High doses, hereditary variations in drug metabolism, and malnutrition predispose to this complication. Spontaneous recovery is the rule when administration of the drug is halted. Isoniazid-induced neuropathy can be prevented by concurrent administration of pyridoxine, 100 mg/d orally.

Phenytoin is often mentioned as a cause of polyneuropathy, but evidence for phenytoin treatment as a cause of symptomatic neuropathy is sparse.

Pyridoxine (vitamin B_6) toxicity has been implicated as the cause of a sensory neuronopathy that disproportionately impairs vibration and position sense. This disorder occurs in patients taking at least 200 mg of pyridoxine daily – about 100 times the minimum daily requirement. Sensory ataxia, Romberg's sign, Lhermitte's sign, and ankle areflexia are common findings. Pain is less common, and motor involvement is unusual. Symptoms are usually reversible

over months to years if the abuse ceases, but an irreversible syndrome has also been reported following intravenous administration of high doses of pyridoxine.

Vincristine produces a polyneuropathy in most patients who receive the drug for treatment of (usually hematologic) cancer. The earliest manifestations are distal sensory symptoms and loss of reflexes. Motor deficits may predominate later in the course, however. Constipation is a common finding and may be due to autonomic involvement. Discontinuing the drug or administering it at a reduced dosage often leads to improvement.

Toxins

Organic compounds implicated as causes of polyneuropathy include hexacarbons present in solvents and glues (eg, n-hexane, methyl n-butyl ketone) and organophosphates used as plasticizers or insecticides (eg, triorthocresyl-phosphate). Sensory involvement is most striking in n-hexane neuropathy, whereas neuropathy caused by triorthocresyl phosphate primarily affects motor nerves.

Heavy metals may also be responsible for polyneuropathy. Neuropathy caused by lead, arsenic, and thallium. Gold, which is used to treat rheumatoid arthritis, may cause a symmetric polyneuropathy, and cisplatin (a platinum analogue with anticancer activity) may produce a sensory neuropathy.

Eosinophilia-myalgia syndrome was first identified in 1989 in patients taking L-tryptophan who developed disabling myalgias with blood eosinophil counts above 1,000/μL. About 85% of patients are women. The cause appears to be 1,1'-ethylidenebis [tryptophan], a contaminant in certain commercial preparations of L-tryptophan, which have since been withdrawn. Symptoms include myalgia, arthralgia, dyspnea, cough, rash, fever, and sclerodermiform skin changes. Neurologic findings include weakness of distal and proximal limb and bulbar muscles, distal sensory loss, and areflexia. Eosinophilia, leukocytosis, and elevated liver enzymes are typical. Nerve conduction studies and electromyography may show evidence of polyneuropathy, myopathy, or both. Inflammation is prominent in skin biopsy specimens, but less so in nerve and muscle, which show primarily axonal degeneration and muscle fiber atrophy. Treatment is discontinuation of L-tryptophan and administration of corticosteroids, nonsteroidal antiinflammatory drugs, and analgesics. Most patients improve or recover fully, but deaths have been reported.

HEREDITARY NEUROPATHIES

Idiopathic

Hereditary motor and sensory neuropathies (HMSN) include the hypertrophic (HMSN type I) and neuronal (HMSN type II) forms of CharcotMarie-Tooth disease as well as Dejerine-Sottas disease (HMSN type III). HMSN type I

is a slowly progressive demyelinating neuropathy that occurs either sporadically or with a dominant, X-linked, or recessive mode of inheritance. Dominant inheritance is the most common pattern, and genetic studies have shown linkage to the short arm of chromosome 17, the long arm of chromosome 1, or the X chromosome. When chromosome 17 is involved (as occurs in most cases), there is duplication of the PMP-22 gene that can be detected in single affected individuals and therefore forms the basis of a useful diagnostic test. On chromosome 1, the myelin protein zero (P0) gene has been implicated, whereas point mutations of the connexin 32 gene have been incriminated in the X-linked form. The nerves may be palpably enlarged. HMSN type II, which is less common, affects the anterior horn cells and thus resembles progressive spinal muscular atrophy. Genetic studies of the autosomal dominant form have shown linkage to chromosome 1p in some cases. HMSN type III is a slowly progressive demyelinating disorder that usually has a recessive mode of inheritance and progresses from its onset in infancy or childhood to cause severe disability by the third decade of life. The nerves are typically enlarged.

Hereditary sensory and autonomic neuropathies (HSAN) also take a variety of forms. In HSAN type I, there is a dominant inheritance, a gradually progressive course from onset in early adulthood, and symmetric loss of distal pain and temperature perception, with relative preservation of light touch. Perforating ulcers over pressure points and painless infections of the extremities are common. The tendon reflexes are depressed, but there is little, if any, motor disturbance. In HSAN type II, inheritance is recessive, onset is in infancy or early childhood, all sensory modalities are affected, and tendon reflexes are lost. HSAN type III (Riley-Day syndrome, familial dysautonomia) is a recessive disorder that commences in infancy and is characterized by conspicuous autonomic dysfunction (absent tearing, labile temperature and blood pressure), accompanied by absent taste sensation, impaired pain and temperature sensation, and areflexia. HSAN type IV is associated with congenital insensitivity to pain and absent sweating.

Polyneuropathy can occur in both the hereditary and nonhereditary forms of amyloidosis. Because small-diameter sensory and autonomic nerve fibers are especially likely to be involved, pain and temperature sensation and autonomic functions are prominently affected. Clinical presentation is commonly with distal paresthesias, dysesthesias, and numbness; postural hypotension; impaired thermoregulatory sweating; and disturbances of bladder, bowel, or sexual function. Distal weakness and wasting eventually occur. The tendon reflexes are often preserved until a relatively late stage. Entrapment neuropathy – especially carpal tunnel syndrome – may develop as a consequence of amyloid deposits. There is no specific treatment.

Friedreich's ataxia usually has a recessive mode of inheritance but occasionally occurs with dominant inheritance. It is caused in many cases by a triplet repeat expansion in a noncoding region of the frataxin gene (X25) on chromo-

some 9q13-q21.1, but there is some heterogeneity of phenotype and variation in age of onset among patients with this expansion. This expansion has not been found in all cases, suggesting that other genetic or environmental factors are sometimes responsible. An ataxic gait develops, followed by clumsiness of the hands and other signs of cerebellar dysfunction. Involvement of peripheral sensory fibers leads to sensory deficits of the limbs, with depressed or absent tendon reflexes. There may also be leg weakness and extensor plantar responses from central motor involvement.

Hereditary neuropathy with liability to pressure palsies is a genetically heterogeneous disorder that relates most commonly to deletion of the PMP-22 gene on chromosome 17. Inheritance is as an autosomal dominant trait with variable expression. Patients present with simple or multiple mononeuropathies that occur after mild pressure or stretch of nerves, and electrophysiologic studies reveal that abnormalities are more widespread than is evident clinically.

Metabolic

In acute intermittent porphyria, which is transmitted by recessive inheritance, the initial neurologic manifestation is often a polyneuropathy that (usually) involves motor more than sensory fibers. Sensory symptoms and signs may be predominantly proximal or distal. The peripheral nerves may also be affected in variegate porphyria.

Two recessive lipidoses are associated with polyneuropathy with a typical onset in infancy or childhood. These are metachromatic leukodystrophy, which results from deficiency of the enzyme arylsulfatase A, and Krabbe's disease, which is due to galactocerebroside β-galactosidase deficiency. Both are inherited in an autosomal recessive fashion.

Lipoprotein deficiencies that cause polyneuropathy include abetalipoproteinemia, which is associated with acanthocytosis, malabsorption, retinitis pigmentosa, and cerebellar ataxia; and Tangier disease, which produces cataract, orange discoloration of the tonsils, and hepatosplenomegaly. These are autosomal recessive conditions.

Refsum's disease is an autosomal recessive disorder related to impaired metabolism of phytanic acid. It produces polyneuropathy, cerebellar ataxia, retinitis pigmentosa, and ichthyosis. It can be treated by restricting dietary intake of phytol. Plasmapheresis to reduce body stores of phytanic acid may also be helpful at the initiation of treatment.

Fabry's disease is an X-linked recessive deficiency of the enzyme a-galactosidase-A. It results in a painful sensory and autonomic neuropathy, angiokeratomas, renal disease, and an increased incidence of stroke. The responsible gene has been localized to the long arm of the X chromosome; mutations causing the disease have been recognized and include gene rearrangements, an RNA-splicing defect, and various exotic lesions. Phenytoin or carbamazepine may be

helpful in treating the pain that characterizes the disorder. Enzyme replacement therapy is under investigation.

ENTRAPMENT NEUROPATHIES

Certain peripheral nerves are particularly susceptible to mechanical injury at vulnerable sites. The term entrapment neuropathy is used when the nerve is compressed, stretched, or angulated by adjacent anatomic structures to such an extent that dysfunction occurs. There are numerous entrapment neuropathies, and in many the initial or most conspicuous clinical complaints are of sensory symptoms or pain. Some of the more common syndromes are described below.

ENTRAPMENT SYNDROMES OF UPPER LIMBS

Median Nerve Compression

Compression of the median nerve can occur in the carpal tunnel at the wrist. Carpal tunnel syndrome is common during pregnancy and can occur as a complication of trauma, degenerative arthritis, tenosynovitis, myxedema, and acromegaly. Early symptoms are pain and paresthesias confined to a median nerve distribution in the hand, ie, involving primarily the thumb, index, and middle fingers and the lateral half of the ring finger. There may be pain in the forearm and, in occasional patients, even in the upper arm, shoulder, and neck. Symptoms are often particularly troublesome at night and may awaken the patient from sleep. As the neuropathy advances, weakness and atrophy may eventually develop in the thenar muscles. Examination reveals impaired cutaneous sensation in the median nerve distribution in the hand and, with motor involvement, weakness and wasting of the abductor pollicis brevis and opponens pollicis muscles. There may be a positive Tinel sign (percussion of the nerve at the wrist causes paresthesias in its distribution) or a positive response to Phalen's maneuver (flexion of the wrist for I minute exacerbates or reproduces symptoms). The diagnosis can generally be confirmed by electrophysiologic studies, showing sensory or motor conduction velocity to be slowed at the wrist; there may be signs of chronic partial denervation in median-supplied muscles of the hand. If the symptoms fail to respond to local corticosteroid injections or simple maneuvers such as wearing a nocturnal wrist splint, surgical decompression of the carpal tunnel may be necessary.

Interdigital Neuropathy

Interdigital neuropathy may lead to pain in one or two fingers, and exami-

nation reveals hyperpathia or impaired cutaneous sensation in the appropriate distribution of the affected nerve or nerves. Such a neuropathy may result from entrapment in the intermetacarpal tunnel of the hand, direct trauma, tenosynovitis, or arthritis. Treatment by local infiltration with corti co steroids is sometimes helpful, but in severe cases neurolysis may be necessary.

Ulnar Nerve Dysfunction

Ulnar nerve dysfunction at the elbow leads to paresthesias, hypes the paresthesias, and nocturnal pain in the little finger and ulnar border of the hand. Pain may also occur about the elbow. Symptoms are often intensified by elbow flexion or use of the arm. Examination may reveal sensory loss on the ulnar aspect of the hand and weakness of the adductor pollicis, the deep flexor muscles of the fourth and fifth digits, and the intrinsic hand muscles. The lesion may result from external pressure, from entrapment within the cubital tunnel, or from cubitus valgus deformity causing chronic stretch injury of the nerve. Electrodiagnostic studies may be helpful in localizing the lesion.

Avoiding pressure on or repetitive flexion and extension of the elbow, combined in some instances with splinting the elbow in extension, is sometimes sufficient to arrest progression and alleviate symptoms. Surgical decompression or ulnar nerve transposition to the flexor surface of the arm may also be helpful, depending on the cause and severity of the lesion and the duration of symptoms.

An ulnar nerve lesion may develop in the wrist or palm of the hand in association with repetitive trauma, arthritis, or compression from ganglia or benign tumors. Involvement of the deep terminal branch in the palm leads to a motor deficit in ulnarinnervated hand muscles other than the hypothenar group, while a more proximal palmar lesion affects the latter muscles as well; there is no sensory deficit. With lesions at the wrist involving either the ulnar nerve itself or its deep and superficial branches, both sensory and motor changes occur in the hand. Sensation over the dorsal surface of the hand is unaffected, however, because the cutaneous branch to this region arises proximal to the wrist. Surgical treatment is helpful in relieving compression from a ganglion or benign tumor.

Radial Nerve Compression

The radial nerve may be compressed in the axilla by pressure from crutches or other causes; this is frequently seen in alcoholics and drug addicts who have fallen asleep with an arm draped over some hard surface. The resulting deficit is primarily motor, with weakness or paralysis occurring in the muscles supplied by the nerve, but sensory changes may also occur, especially in a small region on the back of the hand between the thumb and index finger. Treatment involves preventing further compression of the nerve. Recovery usually occurs spontaneously and completely except when a very severe injury has resulted in axonal degeneration. Physical therapy and a wrist splint may be helpful until recovery occurs.

ENTRAPMENT SYNDROMES OF LOWER LIMBS

Peroneal Nerve Lesions

Peroneal nerve lesions can occur secondary to trauma or to pressure about the knee at the head of the fibula. The resulting weakness or paralysis of foot and toe extension – and foot eversion – is accompanied by impaired sensation over the dorsum of the foot and the lower anterior aspect of the leg. The ankle reflex is preserved, as is foot inversion. Treatment is purely supportive. It is important to protect the nerve from further injury or compression. Patients with foot drop may require a brace until recovery occurs. Recovery occurs spontaneously with time and is usually complete unless the injury was severe enough to cause marked axonal degeneration.

Tarsal Tunnel Syndrome

The posterior tibial nerve or its branches can be compressed between the floor and the ligamentous roof of the tarsal tunnel, which is located at the ankle immediately below and behind the medial malleolus. The usual complaint is of burning in the foot – especially at night – sometimes accompanied by weakness of the intrinsic foot muscles. The diagnosis can usually be confirmed electrophysiologically. If treatment with local injection of steroids is not helpful, surgical decompression may be necessary.

Femoral Neuropathy

Isolated femoral neuropathy may occur in association with diabetes mellitus, vascular disease, bleeding diatheses (eg, hemophilia, treatment with anticoagulant drugs), or retroperitoneal neoplasms. The most conspicuous symptoms and signs relate to weakness of the quadriceps muscle, with reduced or absent knee reflex, but there may also be sensory disturbances in the anterior and medial aspects of the thigh and the medial part of the lower leg. Treatment is of the underlying cause.

Saphenous Nerve Injury

The saphenous nerve is the terminal sensory branch of the femoral nerve and supplies cutaneous sensation to the medial aspect of the leg about and below the knee. Mechanical injury to the nerve can occur at several points along its course; patients then complain of pain or impaired sensation in the distribution of the nerve. Weakness in quadriceps function (ie, extension at the knee) reflects femoral nerve involvement. There is no specific treatment, but the nerve should be protected from further injury.

Lateral Femoral Cutaneous Nerve Dysfunction

The lateral femoral cutaneous nerve supplies sensation to the outer border of the thigh. Its function can be impaired by excessive angulation or compression by neighboring anatomic structures, especially in pregnancy or other conditions that cause exaggerated lumbar lordosis. This leads to pain and paresthesias in the lateral thigh, and examination reveals impaired sensation in this region. This syndrome, known as meralgia paresthetica, is best treated with symptomatic measures, since its course is often self-limited.

Obturator Nerve Injury

Trauma to the obturator nerve – eg, by pelvic fracture or a surgical procedure – can lead to pain radiating from the groin down the inner aspect of the thigh. An obturator hernia or osteitis pubis may cause a similar disorder; there is accompanying weakness of the adductor thigh muscles.

ROOT & PLEXUS LESIONS

BACK & NECK PAIN

Spinal disease occurs most commonly in the neck or low back and can cause local or root pain or both. It can also lead to pain that is referred to other parts of the involved dermatomes. Pain from the lower lumbar spine, for example, is often referred to the buttocks. Conversely, pain may be referred to the back from the viscera, especially the pelvic organs. Local pain may lead to protective reflex muscle spasm, which in turn causes further pain and may result in abnormal posture, limitation of movement, and local spinal tenderness.

The history may provide clues to the underlying cause, and physical examination will define any neurologic involvement. Diagnostic studies that can help in evaluating patients include x-rays of the affected region and a complete blood count and erythrocyte sedimentation rate (especially if infective or inflammatory disorders or myeloma is suspected); determination of serum protein and protein electrophoresis; and measurement of serum calcium, phosphorus, alkaline and acid phosphatase, and uric acid. Electromyography may be helpful in determining the extent and severity of root involvement; it also provides a guide to prognosis. A CT scan, MRI of the spine, or a myelogram may be necessary, especially if neoplasm is suspected, neurologic deficits are progressive, pain persists despite conservative treatment measures, or there is evidence of cord involvement. At myelography, CSF can be obtained for laboratory examination.

1. LOW BACK PAIN

Low back pain is a common cause of time lost from work. It has many causes.

Trauma

Unaccustomed exertion or activity – or lifting heavy objects without adequate bracing of the spine – can cause musculoskeletal pain that improves with rest. Clinical examination commonly reveals spasm of the lumbar muscles and restricted spinal movements. Management includes local heat, bed rest on a firm mattress, nonsteroidal anti-inflammatory drugs or other analgesics, and muscle-relaxant drugs, eg, diazepam, 2 mg three times daily, increased gradually until symptoms are relieved (or to the highest dose tolerated). Vertebral fractures that follow more severe injury and lead to local pain and tenderness can be visualized at radiography. If cord involvement is suspected – eg, because of leg weakness following injury – the patient must be immobilized until radiographed to determine whether fracture – dislocation of the vertebral column has occurred.

Prolapsed Lumbar Intervertebral Disk

This most commonly affects the L5-S1 or the L4-5 disk. The prolapse may relate to injury, but in many patients it commonly follows minor strain or normal activity. Protruded disk material may press on one or more nerve roots and thus produce radicular pain, a segmental motor or sensory deficit, or a sphincter disturbance in addition to a painful stiff back. The pain may be reproduced by percussion over the spine or sciatic nerve, by passive straight leg raising, or by extension of the knee while the hip is flexed. The presence of bilateral symptoms and signs suggests that disk material has protruded centrally, and this is more likely to be associated with sphincter involvement than is lateral protrusion. An L5 radiculopathy causes weak dorsiflexion of the foot and toes, while an S1 root lesion leads to a depressed ankle jerk and weakness of plantar flexion of the foot. In either case, spinal movements are restricted, there is local tenderness, and Lasegue's sign (reproducing the patient's pain on stretching the sciatic nerve by straight leg raising) is positive. The L4 root is occasionally affected, but involvement of a higher lumbar root should arouse suspicion of other causes of root compression. Pelvic and rectal examination and plain x-rays of the spine help to exclude other diseases, such as local tumors or metastatic neoplastic deposits. Symptoms often resolve with simple analgesics, diazepam, and bed rest on a firm mattress for 1-2 weeks, followed by gradual mobilization. Nonsteroidal anti-inflammatory drugs may be helpful for acute back pain but are often ineffective or provide only minor or transient benefits in patients with symptoms or signs of root compression.

Persisting pain, an increasing neurologic deficit, or any evidence of sphincter dysfunction should lead to MRI, CT scanning, or myelography, and surgical treatment if indicated by the results of these procedures. The detection

of structural abnormalities by these imaging procedures does not mandate surgical treatment unless the clinical circumstances are appropriate – degenerative abnormalities are common in asymptomatic subjects, especially with advancing age, and may therefore be of no clinical relevance.

The persistence of low back and root pain despite surgery may have several causes including inadequate decompression, recurrent herniation of disk material, root compression or damage as a result of the operative procedure, surgery at the wrong level, infective or inflammatory complications of surgery, or spinal instability. In many instances, however, no specific cause can be identified and most patients do not require further surgery. Chronic pain in this setting may, however, respond to spinal cord stimulation.

Lumbar Osteoarthropathy

This tends to occur in later life and may cause low back pain that is increased by activity. Radiologic abnormalities vary in severity. In patients with mild symptoms, a surgical corset is helpful, while in more severe cases operative treatment may be necessary. Even minor changes may cause root or cord dysfunction in patients with a congenitally narrowed spinal canal (spinal stenosis), leading to the syndrome of intermittent claudication of the cord or cauda equina. This is characterized by pain – sometimes accompanied by weakness or radicular sensory disturbances in the legs – that occurs with activity or with certain postures and is relieved by rest. In such circumstances, spinal decompression is indicated.

Ankylosing Spondylitis

Backache and stiffness, followed by progressive limitation of movement, characterize this disorder, which occurs predominantly in young men. Characteristic early radiologic findings consist of sclerosis and narrowing of the sacroiliac joints. Treatment is with nonsteroidal anti-inflammatory agents, especially indomethacin or aspirin. Physical therapy, including postural exercises, is also important.

Neoplastic Disease

Extradural malignant tumors are an important cause of back pain and should be suspected if there is persistent pain that worsens despite bed rest. They may eventually lead to cord compression or a cauda equina syndrome, depending upon the level of involvement. There may initially be no change on plain radiographs of the spine, but a bone scan is sometimes revealing. Benign osteogenic tumors also produce back pain, and plain x-rays then show a lytic lesion; treatment is by excision.

Infections

Tuberculous and pyogenic infections of the vertebrae or intervertebral

disks can cause progressive low back pain and local tenderness. While there are sometimes no systemic signs of infection, the peripheral white cell count and erythrocyte sedimentation rate are raised. X-rays may show disk space narrowing and a soft tissue mass, but they are frequently normal initially.

The osteomyelitis requires long-term antimicrobial therapy; surgical debridement and drainage may also be needed. Spinal epidural abscess similarly presents with localized pain and tenderness, sometimes associated with osteomyelitis. Cord compression may occur with the onset of a rapidly progressive flaccid paraplegia. MRI, CT scanning, or myelography and operative treatment are undertaken urgently if there is evidence of cord compression. In early cases without neurologic involvement, treatment with antibiotics alone may be sufficient.

Osteoporosis

Low back pain is a common complaint in patients with osteoporosis, and vertebral fractures may occur spontaneously or after trivial trauma. Pain may be helped by a brace to support the back. It is important that patients keep active and take a diet containing adequate amounts of calcium, vitamin D, and protein. Estrogen therapy may be helpful in postmenopausal women. In special circumstances, calcitonin, sodium fluoride, or phosphate supplements are helpful.

Congenital Anomalies

Minor spinal anomalies can cause pain because of altered mechanics or alignment or because reduction in the size of the spinal canal renders the cord or roots more liable to compression by degenerative or other changes. Children or young adults with congenital defects in spinal fusion (spinal dysraphism) occasionally present with pain, a neurologic deficit in one or both legs, or sphincter disturbances. Treatment is of the underlying disorder. Congenital spinal stenosis may lead to the syndrome of neurogenic claudication, but symptoms usually develop only in later life when minor degenerative changes have come to be superimposed on the congenital anomaly.

Arachnoiditis

Severe pain in the back and legs can result from inflammation and fibrosis of the arachnoid layer of the spinal meninges (arachnoiditis), which may be idiopathic or causally related to previous surgery, infection, myelography, or long-standing disk disease. There is no adequate treatment, but operation may be possible if the arachnoiditis is localized. Spinal cord stimulation may provide symptomatic relief.

Referred Pain

Disease of the hip joints may cause pain in the back and thighs that is enhanced by activity; examination reveals limitation of movement at the joint with

a positive Patrick sign (hip pain on external rotation of the hip), and x-rays show degenerative changes. Aortic aneurysms, cardiac ischemia, visceral and genitourinary disease (especially pelvic disorders in women), and retroperitoneal masses also cause back pain. There are often other symptoms and signs that suggest the underlying disorder. Moreover, there is no localized spinal tenderness or restriction of motility. Treatment is of the underlying cause.

Nonspecific Chronic Back Pain

In many patients whose chronic back pain poses a difficult management problem, there are no objective clinical signs or obvious causes of pain despite detailed investigations. In some cases, the pain may have a postural basis; in others, it may be a somatic manifestation of a psychiatric disorder. Pain that initially had an organic basis is often enhanced or perpetuated by nonorganic factors and leads to disability out of proportion to the symptoms.

Nonsteroidal anti-inflammatory drugs may provide short-term symptomatic relief. There is some controversy about the chronic use of narcotic analgesics in patients with persisting low back pain, but such agents are generally best avoided. Treatment with tricyclic antidepressant drugs is sometimes helpful, and psychiatric evaluation may be worthwhile. Unnecessary surgical procedures must be avoided.

2. NECK PAIN

Neck pain is a common problem in the general population; surveys indicate that approximately one-third of the adult population have experienced it over the previous year and in many instances it lasts for more than 6 months.

Congenital abnormalities of the cervical spine, such as hemivertebrae or fused vertebrae, basilar impression, and instability of the atlantoaxial joint, can cause neck pain. The traumatic, infective, and neoplastic disorders mentioned above as causes of low back pain can also affect the cervical spine and then produce pain in the neck. Rheumatoid arthritis may involve the spine, especially in the cervical region, leading to pain, stiffness, and reduced mobility; cord compression may result from displacement of vertebrae or atlantoaxial subluxation and can be life-threatening if not treated by fixation.

Cervical injuries are an important cause of neck pain. Whiplash flexion-extension injuries have become especially common as a result of automobile accidents. Other occult cervical injuries such as disk clefts and fissures may be responsible for symptoms in some instances, but are difficult to recognize. Management of persistent symptoms following whiplash injuries is controversial. Conservative therapeutic measures are appropriate. Other approaches sometimes advocated include block of cervical facet joints with bupivacaine and injection

into the joints of depot corticosteroids, but the response is variable and often short-lived. Subluxed cervical facet joints are another well-recognized complication of automobile accidents. Even minor trauma may lead to cervical fractures in an apparently ankylosed region in patients with diffuse idiopathic skeletal hyperostosis, but major neurologic deficits are common in such circumstances.

Acute Cervical Disk Protrusion

Patients may present with neck and radicular arm pain that is exacerbated by head movement. The mechanism responsible for the pain is unclear; pressure on nerve roots is unlikely to be the sole cause because pain may resolve with time and conservative measures despite persisting compression. With lateral herniation of the disk, there may also be segmental motor, sensory, or reflex changes, usually at the C6 or C7 level, on the affected side. With more centrally directed herniations, spastic paraparesis and a sensory disturbance in the legs, sometimes accompanied by impaired sphincter function, can occur as a result of cord involvement. The diagnosis is confirmed by CT scan, MRI, or myelography. However, these imaging studies may show abnormalities in asymptomatic subjects in middle or later life, so that any disk protrusion may be incidental and unrelated to patients' symptoms. Electromyography may help to establish that anatomic abnormalities are of functional relevance.

In mild cases, bed rest or intermittent neck traction, followed by immobilization of the neck in a collar for several weeks, often helps. If these measures fail or if there is a significant neurologic deficit, surgical treatment may be necessary.

Cervical Spondylosis

This is an important cause of pain in the neck and arms, sometimes accompanied by a segmental motor or sensory deficit in the arms or by spastic paraparesis.

3. HERPES ZOSTER (SHINGLES)

This viral disorder becomes increasingly common with advancing age, causing an inflammatory reaction in one or more of the dorsal root or cranial nerve ganglia, in the affected root or nerve itself, and in the CSF. There seems to be spontaneous reactivation of varicella virus that remained latent in sensory ganglia after previous infection. Herpes zoster is common in patients with lymphoma, especially following regional radiotherapy. The initial complaint is of a burning or shooting pain in the involved dermatome, followed within 2-5 days by the development of a vesicular erythematous rash. The pain may diminish in intensity as the rash develops. The rash becomes crusted and scaly after a few

days and then fades, leaving small anesthetic scars. Secondary infection is common. The pain and dysesthesias may last for several weeks or, in some instances, may persist for many months (postherpetic neuralgia) before subsiding, especially in the elderly. The increased incidence and severity of postherpetic neuralgia with age may reflect an age-related reduction in virus-specific cell-mediated immunity. It is not clear whether immunocompromise secondary to HIV infection or connective tissue disease predisposes to postherpetic neuralgia. Pain is exacerbated by touching the involved area. Superficial sensation is often impaired in the affected dermatome, and focal weakness and atrophy can also occur. Signs are usually limited to one dermatome, but more are occasionally involved. Mild pleocytosis and an increased protein concentration sometimes occur in the CSF. The most commonly involved sites are the thoracic dermatomes, but involvement of the first division of the fifth cranial nerve, also common, is especially distressing and may lead to corneal scarring and anesthesia, as well as to a variety of other ocular complications. Facial (VII) nerve palsy occurring in association with a herpetic eruption that involves the ear, palate, pharynx, or neck is called Ramsay Hunt syndrome. Other rare complications of herpes zoster include other motor neuropathies, meningitis, encephalitis, myelopathy, and cerebral angiopathy.

There is no specific treatment. Analgesics provide symptomatic relief. Corticosteroids or acyclovir may reduce the duration and severity of the acute eruption, but neither reduces the likelihood that postherpetic neuralgia will occur. Although postherpetic neuralgia can be very distressing, it sometimes responds to treatment with carbamazepine, up to 1200 mg/d; phenytoin, 300 mg/d; or amitriptyline, 10-100 mg at bedtime. Attempts at relieving postherpetic neuralgia by peripheral nerve section are generally unrewarding, but treatment with topically applied local anesthetics is sometimes helpful.

BELL'S PALSY

Bell's palsy is, by definition, an acute lower motor neuron facial palsy of unknown cause. It is generally accepted that there is inflammation and oedema of the nerve in the facial canal but, not surprisingly, there have been few pathological studies. A viral aetiology is suspected. There are conflicting reports of clustering of cases, suggesting an infective aetiology, and recurring reports implicating herpes viruses.

The incidence of Bell's palsy is about 23/100000/annum. It affects both sexes equally and is less frequent in children than adults. It shows relatively weak associations with hypertension and diabetes, particularly in older patients. Recurrence, on the same or opposite side, is relatively common.

The major causes of non-idiopathic acute facial palsy are head injury, multiple sclerosis, sarcoidosis, Guillain-Barre syndrome, and infection, including herpes zoster (Ramsay Hunt syndrome), Lyme disease, and HIV infection. Some of these may cause simultaneous bilateral facial palsies, whereas bilateral idiopathic (i.e. Bell's) palsy is very rare.

Clinical features

The entire course of Bell's palsy may be painless, but frequently patients complain of pain behind the ipsilateral ear, in the mastoid region, for a day or two before the onset of weakness, and this may continue for a week or more. Paralysis develops rapidly and may reach maximum severity within a few hours. Continuing progression for 24-48 hours is not uncommon and rarely may be over as long as 5 days.

All of the muscles on the affected side of the face are involved, but the degree of weakness may range in severity from mild to complete (about 70 per cent of patients). The appearance of even an incomplete palsy, is striking and it is not surprising that it causes the patient and sometimes their medical attendant considerable alarm. In elderly patients, presumably due to greater laxity of supporting tissues, the resultant facial deformity is more evident than in younger patients. The eyebrow droops and cannot be elevated, and the brow looses its furrows and becomes smooth. The lower eyelid everts (ectropion) causing impaired drainage of the tears, which overflow onto the cheek. The eye cannot close voluntarily or on blinking but there will be some lowering of the upper lid due to reflex inhibition of levator palpebrae superioris. The nasolabial fold becomes shallower, the angle of the mouth droops and cannot be retracted, the cheek billows on respiration, and food tends to accumulate between the cheek and teeth. There is mild dysarthria. If the nerve is involved proximal to the point where it is joined by the chorda tympani, or higher still, affecting the nerve to stapedius, then the patient may complain of impaired taste sensation or hyperacusis (an unpleasant quality to louder sounds).

Many patients complain of numbness over the affected side of the face and, sometimes, tongue. This may be objective, in the sense that the patient will say that light-touch and pinprick sensation are less on the affected side. The corneal reflex is always preserved. There is no obvious anatomical explanation for such sensory symptoms and they are usually attributed to distorted perception caused by the drooping musculature, skin, and associated tissues.

Prognosis

In about 80 per cent of patients improvement starts early and there is full recovery within a few weeks from the onset. Pathologically it is presumed that the weakness in these cases is due entirely to conduction block, from segmental demyelination, from which recovery is rapid. In the remaining 20 per cent of patients, in addition to conduction block, there is Wallerian degeneration of some

or all of the axons, and full recovery will not occur, although most patients have a satisfactory cosmetic outcome. Nerve regeneration starts from the point of interruption but re-innervation, and thus functional recovery, does not develop until at least 3 months after the onset of the palsy, and is never complete, leaving some residual weakness. Some of the regenerating axons become misdirected and innervate muscles that they did not originally supply. Thus, movement in one area may be accompanied by associated movement (synkinesis) elsewhere. This and other complications are discussed below.

An incomplete palsy is the most favourable prognostic sign. Adverse features may include advanced age, diabetes, hypetension, severe pain, loss of taste, and hyperacusis, but none is a reliable indicator of prognosis. Neurophysiological studies, particularly if performed more than 1 week after onset, may offer prognostic information. Whether the findings indicate a good or poor prognosis doesn't alter management, and so they are rarely performed in clinical practice.

Complications

Associated movements (synkinesis) are the result of aberrant re-innervation by regenerating axons. Common patterns include eye closure on lip movement, or elevation of the angle of the mouth on blinking or when the eyebrow is raised. Occasionally the synkinetic movements may be very extensive.

There may also be aberrant parasympathetic nerve re-innervation, giving rise to the phenomenon of crocodile tears-profuse watering of the affected eye when eating. The simplest explanation is that regenerating fibres destined to innervate the submandibular salivary glands become misdirected and reach the lacrimal gland. An alternative explanation is that glossopharyngeal nerve fibres, destined for the parotid gland, in the lesser superficial petrosal nerve send branches to the greater superficial petrosal nerve, where they lie close together, and then innervate the lacrimal gland.

When recovery is incomplete there is often some contracture of the affected muscles. This may be evident as narrowing of the palpebral fissure or deepening of the nasolabial fold.

Treatment

It is likely that the outcome of Bell's palsy is determined within days of the onset. If the inflammation and oedema of the facial nerve causes only conduction block, then full recovery will occur independent of treatment. If the inflammatory process is more severe and results in axonal degeneration, then recovery will be incomplete. Thus, the aim of treatment must be to reduce the oedema and self-compression of the nerve within its bony canal before axonal degeneration occurs. It is impossible, on available evidence, to commend surgical decompression. To be effective it would have to be performed within days of the onset of the palsy. There are no clinical or neurophysiological pointers in those first few days to which patients are going to have a poor prognosis, and it would

clearly be unjustified to operate on all patients given that the vast majority will, in any case, have a satisfactory outcome.

Whether or not corticosteroids are helpful remains an unanswered question. In the absence of contraindications it is very common practice for patients seen within 1 week of onset of the palsy to be given a short course of oral steroids. A typical regimen might start with prednisolone 1 mg/kg body weight/day, with gradually diminishing doses over the next 10-14 days.

The normal tear film is disturbed in Bell's palsy. Despite anatomical considerations, a dry eye or underproduction of tears due to denervation of the lacrimal gland is very uncommon. Rather, tear drainage is affected due to the ectropion and this, together with reduced blinking, often causes mistiness of vision and associated patient anxiety. Corneal sensation is normal and corneal damage is rare in Bell's palsy. Tarsorrhaphy is rarely required but the patient may find it more comfortable to tape the eye closed in bed, and to use glasses to protect the eye from dust and wind. If tear production is impaired, methylcellulose eye drops should be used.

There is no effective treatment for synkinetic movements. In those few patients with severe residual weakness, various plastic surgery procedures can improve the cosmetic appearance. Because of the slow rate of nerve regeneration, no surgical intervention, except occasionally tarsorrhaphy, should be considered until at least 6, and probably 12, months after the onset of the palsy.

Crocodile tears may be treated by section of the tympanic nerve which carries the glossopharyngeal salivary fibres.

A major element in the management of Bell's palsy is reassurance of the patient and detailed explanation of what has happened and the generally favourable prognosis. There is no good evidence that physiotherapy or electrical stimulation are of specific value. However, some patients benefit from taking an active part in the management of their problem, for example by regularly massaging their face or exercising it in front of a mirror.

TRIGEMINAL NEURALGIA

This is the most frequently encountered disorder of the trigeminal nerve. It may be symptomatic of an underlying structural disorder affecting the nerve, but in the majority of patients no specific cause is identified. It is more common in the second half of life, cases in younger people more often being symptomatic, is slightly more frequent in women, and has an overall prevalence of the order of 3-5 per 100 000 population.

Clinical features

These are highly characteristic, but despite this the diagnostic label is frequently applied erroneously to many other causes of facial pain, particularly atypical facial pain and dental disease. In trigeminal neuralgia, pain, typically very severe, occurs in paroxysms, each episode lasting only a few seconds. The frequency of attacks may vary from several in a minute to days between episodes, and in the early stages spontaneous remission for months or years may occur. Unfortunately, permanent remission is rare and with time the bouts of pain become more frequent. Patients often provide graphic descriptions which indicate the severity and quality of the pain-like a dagger, or red hot needle, or poker. Clinicians use the word lancinating. When attacks are frequent, secondary depression is common. Many patients identify one or more triggers to their attacks. These include touching a very specific part of the face, a cold draught, talking, swallowing, chewing, and brushing their teeth. Tactile triggers may prevent the patient washing their face or shaving.

The pain is strictly within the trigeminal distribution, most commonly in the maxillary and mandibular divisions. The ophthalmic division is involved in less than 10 per cent of cases. Typically, pain is felt in only part of the region supplied by the affected division, at least initially, but may then spread to the rest of the divisional area. In later stages both the mandibular and maxillary areas may become involved, but spread to the ophthalmic area is unusual.

Between the paroxysms, particularly if they are frequent, there may be a dull background ache that is not severe. Trigeminal neuralgia never causes continuous discomfort without the characteristic paroxysms. The stabs of pain may be accompanied by involuntary contraction of the facial muscles, giving rise to the synonymous term 'tic douloureux'. Occasional patients develop typical symptoms bilaterally but do not experience bilateral pain at the same time. Physical examination is normal in idiopathic trigeminal neuralgia. Abnormal physical signs suggest symptomatic trigeminal neuralgia.

Aetiology

It has long been recognized that trigeminal neuralgia may be symptomatic of underlying disease. Thus, about 4 per cent of patients with multiple sclerosis experience it, although it is very rare as a presenting symptom. Primary tumours of the trigeminal nerve and compression of the nerve (e.g. by a tumour or aneurysm) very rarely produce symptoms identical to those of trigeminal neuralgia, but more commonly produce complaints of continuous pain or numbness, and on examination abnormal physical signs can be detected.

Excluding these rare causes of symptomatic trigeminal neuralgia one is left with a majority of patients in whom no physical cause is readily apparent, and thus the disorder might be considered to be one of altered function rather

than structure. However, it has been suggested that in a significant number of these patients (over 90 per cent) the cause is a misdirected or ectatic blood vessel in the posterior fossa compressing the trigeminal sensory roots, and that symptomatic improvement can be gained by surgically separating the root from the aberrant blood vessels. In another series, vascular compression was found in only 11 per cent of patients. Increasingly sensitive MRI techniques may shed further light on this issue-scans may show vessels apparently impinging on the trigeminal nerve, but a cause-effect relationship remains to be proved.

Differential diagnosis

Rare symptomatic causes of trigeminal neuralgia have been discussed above and it was noted that they are often accompanied by abnormal physical signs. A substantial number of patients initially diagnosed as having trigeminal neuralgia prove to have other conditions. By far the most common confusion centres around the teeth. Dental disease, such as apical abscess, may cause paroxysmal as well as continuous pain, but the overall features and specific trigger factors should readily distinguish this from trigeminal neuralgia. Conversely, every specialist will have seen patients with trigeminal neuralgia who have had healthy teeth removed. Apart from dental disease, referred facial pain may be caused by sinus disease and eye disease (e.g. glaucoma). Angina may cause lower jaw pain.

Other causes of trigeminal nerve-related pain, which can be distinguished from trigeminal neuralgia on the basis of the history and physical signs, include brainstem lesions, postherpetic neuralgia, and tabes dorsalis. Local irritative lesions and trauma in the regions of exit from the skull of the supraorbital and infraorbital nerves can cause localized neuralgic pain.

Facial pains attributed to temporomandibular joint dysfunction (Costen's syndrome) and maladjustment of the bite are possibly overdiagnosed. Atypical facial pain, despite its name, is a characteristic disorder seen mainly in young and middle-aged women. They complain of a dull, constant ache in the upper jaw/cheek region which may extend to the whole of the side of the head and down into the neck. Often, but not always, there is clear evidence of an anxiety or depressive disorder. There may be a response to antidepressant drugs.

Cluster headache (migrainous neuralgia) is a highly characteristic condition that really should not be confused with trigeminal neuralgia, but sometimes is. The duration, distribution and characteristics of the pain, the different triggering factors, the accompanying symptoms, and the pattern of attacks distinguish the condition from trigeminal neuralgia. Glossopharyngeal neuralgia causes attacks of identical character but in a different distribution.

Treatment

Carbamazepine gives good or excellent symptomatic relief in up to 70 per cent of patients. A reasonable starting dose is 100 mg twice daily increasing, as required, over a 1-2 week period to either the lowest effective dose or the maximal tolerable dose. This is a much more rapid increase than would be used for treating epilepsy (and is done because of the frequency and severity of the attacks) and consequently side-effects are more common, although patients may be happy to trade these off against the relief from pain. Common dose-related sideeffects include nausea, unsteadiness, and visual disturbance. Up to 10 per cent of patients develop an idiosyncratic drug rash which usually necessitates stopping the drug.

If carbamazepine does not work or cannot be tolerated, other drugs that can be tried include sodium valproate, phenytoin, lamotrigine, clonazepam, and baclofen, but success rates are much lower than with carbamazepine.

Spontaneous remission may occur, especially in the early stages. Therefore, if drug treatment leads to resolution of symptoms, it is appropriate to attempt discontinuing treatment when the patient has been pain free for several weeks.

In some patients even very determined attempts with drug treatment prove unsuccessful, whereas in others there may be partial or complete relief but only at the cost of unacceptable side-effects. In such circumstances some form of surgical intervention should be considered.

If the pain is localized within the distribution of a single peripheral nerve (e.g. supraorbital or infraorbital), relief for up to 18 months may be obtained by sectioning the nerve or by injecting the nerve or trigeminal ganglion with alcohol or phenol. Such techniques have largely been superseded by radio frequency thermal coagulation of the trigeminal ganglion, in which an electrode is inserted percutaneously, through the foramen ovale, into the ganglion. Pain appreciation may be abolished, while preserving light-touch. Most patients have good initial relief of pain but late recurrence is not uncommon. The procedure can be repeated.

Posterior fossa exploration, looking for neurovascular abnormalities, has been discussed above. Success rates over 90 per cent have been reported, but others have been less impressed and recurrence rates may be high. If a neurovascular abnormality is not identified, an alternative approach during posterior fossa surgery is partial trigeminal nerve root section, which will produce complete numbness in the relevant areas.

A recent review concluded that radio frequency rhizotomy is the treatment of choice for most patients undergoing a first operative procedure for V2 and V3 neuralgia, but that microvascular decompression is more appropriate for V1 neuralgia because there is a lower risk of corneal anaesthesia.

An area of numbness rather than pain might seem to be an acceptable exchange, but up to 10 per cent of patients develop extremely distressing dysaesthesiae in the anaesthetic area and this is very resistant to treatment. A further complication is that of keratitis, if the surgical treatment produces anaesthesia in the ophthalmic nerve territory. These complications are more likely to occur if there is extensive surgically induced sensory loss, but conversely the less sensory impairment there is, the higher the risk of recurrence of trigeminal neuralgia.

STROKE AND VASCULAR DEMENTIA

Stroke is the third or second most common cause of death in different countries and the most common disabling neurologic disorder. Its incidence increases with age and is somewhat higher in men than in women and in African-Americans than in Caucasians. Risk factors for stroke include systolic or diastolic hypertension, hypercholesterolemia, cigarette smoking, heavy alcohol consumption, and oral contraceptive use. Despite its importance as a leading cause of disability and death, the incidence of stroke has decreased in recent decades, largely because of improved treatment of hypertension.

Stroke is a syndrome characterized by the acute onset of a neurologic deficit that persists for at least 24 hours, reflects focal involvement of the central nervous system, and is the result of a disturbance of the cerebral circulation. The acute onset and subsequent duration of symptoms are documented by the history. The site of central nervous system involvement is suggested by the nature of the symptoms. It is delineated more precisely by the neurologic examination and confirmed by imaging studies (CT scans or MRI). A vascular etiology may be inferred from the acute onset of symptoms and often from the patient's age, the presence of risk factors for stroke, and the occurrence of symptoms and signs referable to the territory of a particular cerebral blood vessel. When this is confirmed by imaging studies, further investigations can be undertaken to identify a specific cause.

Acute Onset

Strokes begin abruptly. Neurologic deficits may be maximal at onset, as is common in embolic stroke, or may progress over seconds to, hours (or occasionally days), which is characteristic of progressive arterial thrombosis or recurrent emboli. A stroke that is actively progressing as a direct consequence of the underlying vascular disorder (but not because of associated cerebral edema) or has done so in recent minutes is termed stroke in evolution or progressing stroke. Focal cerebral deficits that develop slowly (over weeks to months) are unlikely to be due to stroke and are more suggestive of tumor or inflammatory or degenerative disease.

Duration of Deficits

By definition, stroke produces neurologic deficits that persist for at least 24 hours. When symptoms and signs resolve completely after briefer periods (usually within 30 minutes), the term transient ischemic attack (TIA) is used. Recurrent TIAs with identical clinical features are usually caused by thrombosis or embolism arising within the cerebral circulation. TIAs that differ in character

from event to event suggest recurrent emboli from a cardiac source. Although TIAs do not themselves produce lasting neurologic dysfunction, they are important to recognize because about one-third of patients with TIAs will go on to have a stroke within 5 years – and because this risk may be reduced with treatment.

In some cases, deficits last for longer than 24 hours but resolve completely or almost completely within a few days; the term reversible ischemic neurological deficit (RIND) or minor stroke is sometimes used to describe these events. As their names imply, TIAs and RINDs are uniquely associated with cerebral ischemia, as opposed to hemorrhage.

Focal Involvement

Stroke produces focal symptoms and signs that correlate with the area of the brain supplied by the affected blood vessel. In ischemic stroke, occlusion of a blood vessel interrupts the flow of blood to a specific region of the brain, interfering with neurologic functions dependent on that region and producing a more or less stereotyped pattern of deficits. Hemorrhage produces a less predictable pattern of focal involvement because complications such as increased intracranial pressure, cerebral edema, compression of brain tissue and blood vessels, or dispersion of blood through the subarachnoid space or cerebral ventricles can impair brain function at sites remote from the hemorrhage.

Cerebrovascular disorders can also affect the brain in more diffuse fashion and produce global cerebral dysfunction, but the term ***stroke*** should not be applied in these cases. These disorders include **global cerebral ischemia** (usually from cardiac arrest) and **subarachnoid hemorrhage**. In most cases of stroke, the history and neurologic examination provide enough information to localize the lesion to one side of the brain (eg, to the side opposite a hemiparesis or hemisensory deficit or to the left side if aphasia is present) and to the anterior or posterior cerebral circulation.

A. Anterior Circulation. The anterior cerebral circulation, which supplies most of the cerebral cortex and subcortical white matter, basal ganglia, and internal capsule, consists of the internal carotid artery and its branches: the anterior choroidal, anterior cerebral, and middle cerebral arteries. The middle cerebral artery in turn gives rise to deep, penetrating lenticulostriate branches. The specific territory of each of these vessels is shown in Table. Anterior circulation strokes are commonly associated with symptoms and signs that indicate hemispheric dysfunction, such as aphasia, apraxia, or agnosia. They also produce hemiparesis, hemisensory disturbances, and visual field defects, which can also occur with posterior circulation strokes.

B. Posterior Circulation. The posterior cerebral circulation supplies the brainstem, cerebellum, and thalamus and portions of the occipital and temporal lobes. It consists of the paired vertebral arteries, the basilar artery, and their branches: the posterior inferior cerebellar, anterior inferior cerebellar, superior

cerebellar, and posterior cerebral arteries. The posterior cerebral artery also gives off thalamoperforate and thalamogeniculate branches. Posterior circulation strokes produce symptoms and signs of brainstem dysfunction, including coma, drop attacks (sudden collapse without loss of consciousness), vertigo, nausea and vomiting, cranial nerve palsies, ataxia, and crossed sensorimotor deficits that affect the face on one side of the body and the limbs on the other. Hemiparesis, hemisensory disturbances, and visual field deficits also occur, but are not specific to posterior circulation strokes.

Vascular Origin

Although other pathologic processes such as hypoglycemia or other metabolic disturbances, trauma, and seizures can produce focal central neurologic deficits that begin abruptly and last for at least 24 hours, the term ***stroke*** is used only when such events are caused by cerebrovascular disease. The underlying pathologic process in stroke can be either ischemia or hemorrhage, usually from an arterial lesion. In recent series, ischemia accounted for about two-thirds and hemorrhage for about one-third of strokes. It may not be possible to distinguish between ischemia and hemorrhage from the history and neurologic examination, but CT scan or MRI permits a definitive diagnosis.

A. Ischemia. Interruption of blood flow to the brain deprives neurons and other cells of substrate glucose and oxygen and, unless blood flow is promptly restored, leads ultimately to cell death. The pattern of cell death depends on the severity of ischemia. With mild ischemia, as may occur in cardiac arrest with reperfusion, selective vulnerability of certain neuronal populations results in their preferential loss. More severe ischemia produces selective neuronal necrosis, in which all neurons die but glia and endothelial cells are preserved. Complete, permanent ischemia causes pannecrosis, affecting all cell types, and results in the chronic cavitary brain lesions seen after clinical stroke.

Ischemic neuronal injury is an active biochemical process that evolves over time. Lack of glucose and oxygen depletes the cellular energy stores required to maintain membrane potentials and transmembrane ion gradients. Potassium leaks out of cells, causing depolarization-induced calcium entry, and also stimulates the release of glutamate through glial glutamate transporters. Synaptic glutamate activates excitatory amino acid receptors coupled to calcium- and sodium-preferring ion channels. The resulting influx of sodium into postsynaptic neuronal cell bodies and dendrites causes depolarization and acute swelling. Calcium influx that exceeds the ability of the cell to extrude, sequester, or buffer calcium activates calcium-dependent enzymes (pro teases, lipases, and nucleases). These enzymes and their metabolic products, such as eicosanoids and oxygen free radicals, cause the breakdown of plasma membranes and cytoskeletal elements, leading to cell death. This sequence of events has been termed excitotoxicity because of the pivotal role of excitatory amino acids such as glutamate.

Where ischemia is incomplete and therefore permits more prolonged cell survival – as in the border zone or penumbra surrounding the core of an ischemic brain region-other biochemical processes that regulate cell death may be set into motion. These include the expression of proteins involved in programmed cell death, such as Bcl (B-cell lymphoma)-2-family proteins and caspases (proenzymes for cysteine proteases that cleave at aspartate residues). The action of these proteins leads to apoptosis, a form of cell death that is distinct from necrosis, and is characterized by margination of nuclear chromatin, cleavage of DNA into fragments of defined length (nucleosomes), relative preservation of cell membrane integrity, blebbing of the plasma membrane to form apoptotic bodies, and phagocytosis without inflammation.

If the blood flow to ischemic brain tissue is restored before neurons are irreversibly injured, the clinical symptoms and signs are transient. Prolonged interruption of blood flow, however, leads to irreversible ischemic injury (infarction) and persistent neurologic deficits.

Two pathogenetic mechanisms can produce ischemic stroke-thrombosis and embolism. While about two – thirds of ischemic strokes are attributed to thrombosis and about one-third to embolism, the distinction is often difficult or impossible to make on clinical grounds.

1. Thrombosis produces stroke by occluding large cerebral arteries (especially the internal carotid, middle cerebral, or basilar), small penetrating arteries (as in lacunar stroke), cerebral veins, or venous sinuses. Symptoms typically evolve over minutes to hours. Thrombotic strokes are often preceded by TIAs, which tend to produce similar symptoms because they affect the same territory recurrently.

2. Embolism produces stroke when cerebral arteries are occluded by the distal passage of thrombus from the heart, aortic arch, or large cerebral arteries. Emboli in the anterior cerebral circulation most often occlude the middle cerebral artery or its branches, since about 85% of the hemispheric blood flow is carried by this vessel. .Emboli in the posterior cerebral circulation usually lodge at the apex of the basilar artery or in the posterior cerebral arteries. Embolic strokes characteristically produce neurologic deficits that are maximal at onset. When TIAs precede embolic strokes, especially those arising from a cardiac source, symptoms typically vary between attacks since different vascular territories are affected.

B. Hemorrhage. Hemorrhage may interfere with cerebral function through a variety of mechanisms, including destruction or compression of brain tissue and compression of vascular structures, leading to secondary ischemia and edema. Intracranial hemorrhage is classified by its location as intracerebral, subarachnoid, subdural, or epidural, all of which-except subdural hemorrhage-are usually caused by arterial bleeding.

1. Intracerebral hemorrhage causes symptoms by compressing adjacent tissue (which can then produce local ischemia) and, to a lesser extent, by de-

stroying tissue. Unlike ischemic stroke, intracerebral hemorrhage tends to cause more severe headache and depression of consciousness as well as neurologic deficits that do not correspond to the distribution of any single blood vessel.

2. Subarachnoid hemorrhage leads to cerebral dysfunction by elevating intracranial pressure as well as by exerting still poorly understood toxic effects of subarachnoid blood on brain tissue. In addition, subarachnoid hemorrhage may be complicated by vasospasm (leading to ischemia), rebleeding, extension of blood into brain tissue (producing an intracerebral hematoma), or hydrocephalus. Subarachnoid hemorrhage typically presents with headache rather than focal neurologic deficits.

3. Subdural or epidural hemorrhage produces a mass lesion that can compress the underlying brain. These hemorrhages are often traumatic in origin, and usually present with headache or altered consciousness.

FOCAL CEREBRAL ISCHEMIA

Etiology

A variety of disorders of the blood, blood vessels, and heart can lead to focal cerebral ischemia. Conditions associated with focal cerebral ischemia:

Vascular disorders
- Atherosclerosis
- Fibromuscular dysplasia
- Inflammatory disorders
  - Giant cell arteritis
  - Systemic lupus erythematosus
  - Polyarteritis nodosa
  - Granulomatous angiitis
  - Syphilitic arteritis
  - AIDS
- Carotid or vertebral artery dissection
- Lacunar infarction
- Drug abuse
- Migraine
- Multiple progressive intracranial occlusions (moyamoya syndrome)
- Venous or sinus thrombosis

Cardiac disorders
- Mural thrombus
- Rheumatic heart disease
- Arrhythmias
- Endocarditis

Mitral valve prolapse
Paradoxic embolus
Atrial myxoma
Prosthetic heart valves

Hematologic disorders

Thrombocytosis
Polycythemia
Sickle cell disease
Leukocytosis
Hypercoagulable states

A. Vascular Disorders

1. Atherosclerosis. In most cases, atherosclerosis of the large extracranial arteries in the neck and at the base of the brain is the underlying cause of focal cerebral ischemia. The sites of predilection are the origin of the common carotid artery, the internal carotid artery just above the common carotid bifurcation and within the cavernous sinus, the origin of the middle cerebral artery, the vertebral artery at its origin and just above where it enters the skull, and the basilar artery.

The pathogenesis of atherosclerosis is incompletely understood, but injury to vascular endothelial cells is thought to be an early step. Endothelial cells may be injured by the accumulation of cholesterol esters derived from circulating low-density lipoproteins or by other mechanical, biochemical, or inflammatory mechanisms. Blood monocytes, macrophages, and T lymphocytes adhere to the sites of endothelial injury or denudation and subsequently migrate subendothelially, where they are transformed into lipid-laden foam cells. The resulting lesion is called a fatty streak. The release of growth and chemotactic factors from endothelial cells and monocytic macrophages stimulates the proliferation and migration of intimal smooth muscle cells, and leads to formation of a fibrous plaque. Further endothelial injury or denudation ensues, promoting the adherence of platelets, which also release growth and chemotactic factors. The resulting atheromatous lesion may enlarge to occlude the vessel lumen, or it may provide a source of atheromatous or platelet emboli. Ulcerated atheromas may be especially likely sources of emboli.

The most important risk factor for atherosclerosis leading to stroke is systolic or diastolic hypertension. In one study of more than 5000 symptom-free men and women aged from 30 to 60 years followed prospectively for 18 years, the likelihood of hypertensive subjects developing stroke was seven times that of the nonhypertensives. Furthermore, the incidence of all the major cardiac and cerebrovascular sequelae of hypertension increased in direct proportion to the blood pressure even in the nonhypertensive range, without any identifiable critical or safe value. A blood pressure of 160 mm Hg systolic or 95 mm Hg diastolic observed during any clinic visit tripled the risk of stroke, suggesting that such patients should receive antihypertensive treatment.

Atherosclerosis can also occur in the absence of hypertension. In such cases, other factors such as diabetes, elevated serum cholesterol and triglycerides, hyperhomocysteinemia, cigarette smoking, hereditary predisposition, and the use of oral contraceptives may be implicated. Genetic disorders associated with accelerated atherosclerosis include homocystinuria and dyslipoproteinemias.

2. Fibromuscular dysplasia. This is a segmental nonatherosclerotic condition of large arteries characterized by segmental thinning of the media and fragmentation of the elastic lamina, alternating with rings of fibrous and muscular hyperplasia within the media. In at least some families, fibromuscular dysphasia is inherited in autosomal dominant fashion and has been mapped to a site on chromosome 2 (2q31). Systemic involvement may produce limb claudication, hypertension from renal artery hyperplasia, or myocardial infarction. Extracranial vessels are involved more often than intracranial ones, and the cervical portion of the internal carotid is involved more than is the vertebral artery. Lesions are often bilateral, and women are more often affected than men. Transitory or fixed cerebral ischemic deficits may occur, although complete occlusion of involved arteries is rare, suggesting that symptoms may be due to the embolization of vascular thrombi. There is a characteristic string-ofbeads appearance on angiography, indicating the presence of saccular dilations of involved arteries. The disorder is associated with saccular aneurysms of the cerebral arteries, which can in turn produce subarachnoid hemorrhage. Cerebral ischemic complications of fibromuscular dysplasia may be reduced by treatment with aspirin or by graduated intraluminal dilation of the affected extracranial vessels in symptomatic cases.

3. Inflammatory disorders

a. Giant cell arteritis, also called temporal arteritis or cranial arteritis, sometimes produces signs of cerebral ischemia. Inflammatory changes affect the branches of the external carotid, cervical internal carotid, posterior ciliary, extracranial vertebral, and intracranial arteries. Inflammatory changes in the arterial wall may stimulate platelet adhesion and aggregation on damaged surfaces, leading to thrombosis or distal embolism. Physical examination may show tender, nodular, or pulseless temporal arteries. Laboratory findings include an increased erythrocyte sedimentation rate and evidence of vascular stenosis or occlusion on angiography or color duplex ultrasonography. Definitive diagnosis is by temporal artery biopsy. Although it is an uncommon cause of cerebral ischemic symptoms, giant cell arteritis should be considered in patients with transient monocular blindness or transient cerebral ischemic attacks – especially elderly patients – because the disorder is responsive to corticosteroid therapy and its complications (especially permanent blindness) may thus be avoided.

b. Systemic lupus erythematosus is associated with a vasculopathy that involves small cerebral vessels and leads to multiple microinfarctions. Inflammatory changes characteristic of true vasculitis are absent. There is no correla-

tion between cerebral microinfarcts and verrucous (Libman-Sacks) endocarditis; cardiac emboli therefore appear to play little or no role in the genesis of cerebral symptoms.

c. Polyarteritis nodosa is a segmental vasculitis of small and medium-sized arteries that affects multiple organs. Transient symptoms of cerebral ischemia, including typical spells of transient monocular blindness, can occur.

d. Granulomatous angiitis (also called primary angiitis of the central nervous system) is an idiopathic inflammatory disease that affects small arteries and veins in the central nervous system and can cause transient or progressive multifocal lesions. Clinical features include headache, hemiparesis and other focal neurologic abnormalities, and cognitive disturbances. The CSF usually shows pleocytosis and elevated protein, but the erythrocyte sedimentation rate is typically normal. The diagnosis should be suspected in any patient with multifocal central nervous system dysfunction and CSF pleocytosis. Angiography demonstrates focal and segmental narrowing of small arteries and veins, and a meningeal biopsy is diagnostic. Treatment with corticosteroids, alone or in combination with cyclophosphamide, may be beneficial.

e. Syphilitic arteritis is uncommon but is being seen with increasing frequency in the male homosexual and other at-risk populations. It generally occurs within 5 years after the initial infection and reflects the underlying meningeal inflammatory process. It is important to recognize and treat the disorder at this early stage to prevent the later development of tertiary parenchymal neurosyphilis (general paresis or tabesdorsalis). Medium-sized penetrating vessels are typically involved, producing punctate areas of infarction in the deep white matter of the cerebral hemisphere, that can be seen on CT scan or MRI.

f. AIDS is associated with an increased incidence of TIAs and ischemic stroke. The reason for this association is unclear, but the toxic effects of HIV – 1 on blood vessels or the deposition of immune complexes may be involved. In some cases, ischemic neurologic complications of AIDS are associated with endocarditis or with opportunistic infections of the central nervous system, such as toxoplasmosis or cryptococcal meningitis.

4. Carotid or vertebral artery dissection. Dissection of the carotid or vertebral artery is associated with hemorrhage into the vessel wall, which can occlude the vessel or predispose to thrombus formation and embolization. Posttraumatic carotid dissections present little difficulty in diagnosis. Certain patients, however – usually young men – suffer cerebral infarction after apparently spontaneous carotid artery dissection. Internal carotid artery dissections usually originate near the carotid bifurcation and can extend to the base of the skull. The underlying pathologic process is usually cystic medial necrosis. Prodromal transient hemispheric ischemia or monocular blindness sometimes precedes a devastating stroke. Carotid dissection may be accompanied by pain in the jaw or neck, visual abnormalities akin to those that occur in migraine, or Homer's syndrome.

Dissection of the vertebral or basilar artery is less common. The clinical features of this disorder include headache, posterior neck pain, and the sudden onset of signs of brainstem dysfunction.

The treatment of carotid or vertebral artery dissection is controversial. Approaches include no treatment, removal of the intramural hematoma, and measures to prevent embolization from the site of dissection (aspirin, anticoagulants, or occlusion of the vessel distal to the dissection). Recurrent dissection is uncommon and usually occurs within 1 month of the initial event.

5. Lacunar infarction. Lacunar infarction of the brain results from the occlusion of small penetrating branches of the major cerebral arteries, especially those that supply the basal ganglia, thalamus, internal capsule, and pons. Lacunar infarcts are believed to be caused by either atherosclerosis or degenerative changes in arterial walls (including lipohyalinosis and fibrinoid necrosis) that are related to long-standing hypertension. Both hypertension and diabetes appear to predispose to this type of stroke.

6. Drug abuse. Recreational use of cocaine hydrochloride, alkaloidal (crack) cocaine, amphetamines, or heroin appears to be a common risk factor for stroke in patients less than 35 years old. Patients who take these agents intravenously may develop infective endocarditis (see below) leading to embolic stroke. Stroke also occurs in drug users without endocarditis, however, including those who take drugs only intranasally or by smoke or vapor inhalation, and often has its onset within hours of drug use. Mechanisms that have been proposed to explain these events include drug-induced vasospasm, vasculitis, and the rupture of preexisting aneurysms or vascular malformations. Cocaine hydrochloride is most often associated with intracerebral hemorrhage but can also cause subarachnoid hemorrhage or ischemic stroke. Stroke from crack cocaine is most commonly ischemic in origin, but intracerebral or subarachnoid hemorrhage also occurs. Amphetamines can produce vasculitis, with necrosis of the vessel wall leading to intracerebral hemorrhage; ischemic stroke and subarachnoid hemorrhage are less frequent. Heroin is associated primarily with embolic stroke resulting from endocarditis.

7. Multiple progressive intracranial arterial occlusions (moyamoya). This syndrome has two essential features: bilateral narrowing or occlusion of the distal internal carotid arteries and the adjacent anterior and middle cerebral artery trunks; and the presence of a fine network of collateral channels at the base of the brain. The term ***moyamoya*** derives from a Japanese word meaning ***smoke*** or ***haze***, which characterizes the angiographic appearance of these fine collaterals. Moyamoya is most common in Japanese girls and is sometimes inherited as an autosomal recessive disorder, but occurs in all ethnic groups and in patients with atherosclerosis, sickle cell anemia, or a history of basilar meningitis. The term therefore denotes an angiographic pattern of collateral vessels rather than a clinical or pathologic syndrome. Children tend to present with ischemic

strokes; adults present with intracerebral, subdural, or subarachnoid hemorrhage. Transient episodes of cerebral ischemia are infrequent.

8. Migraine. Stroke is a rare complication of migraine. Migrainous stroke occurs during an attack of classic migraine and in the same vascular territory affected by previous migraine attacks. The anterior (especially middle cerebral artery) and posterior (especially posterior cerebral artery) cerebral circulations are affected about equally often. Investigative studies show no other cause of stroke (eg, occlusion of large cerebral arteries), suggesting that migraine itself is the cause, although other stroke risk factors (eg, oral contraceptive use) may exist.

9. Venous or sinus thrombosis. This uncommon cause of stroke is typically associated with a predisposing condition such as otitis or sinusitis, a postpartum state, dehydration, or coagulopathy. Clinical features include headache, papilledema, impaired consciousness, seizures, and focal neurologic deficits. CSF pressure is typically increased, and in cases of septic thrombosis, pleocytosis may occur. A CT scan may demonstrate hemorrhage associated with venous infarction, and in superior sagittal sinus thrombosis a CT scan with contrast sometimes shows a filling defect corresponding to the clot (delta sign). However, MRI with contrast is the diagnostic procedure of choice in most cases. The diagnosis may be confirmed by MR angiography, but conventional intra-arterial x-ray angiography is now rarely indicated. In patients presenting with headache and papilledema, venous or sinus thrombosis must be differentiated from intracranial mass lesions and idiopathic pseudotumor cerebri. The radiologic studies mentioned above are useful in this regard. Septic thromboses are treated with antibiotics. Anticoagulation has been used for aseptic thrombosis, but its efficacy has not been proved, and it may precipitate intracranial hemorrhage.

B. Cardiac Disorders

1. Mural thrombus. Mural thrombus complicating myocardial infarction or cardiomyopathy is a recognized source of cerebral embolism. The risk of stroke in the first weeks after myocardial infarction is related to the size of the cardiac lesion. More extensive myocardial damage may increase the tendency for mural thrombi to form; it may exacerbate the generalized hypercoagulable state that accompanies the infarct – or it may do both. Accordingly, patients with large transmural myocardial infarcts require anticoagulation therapy to substantially reduce the incidence of early thromboembolic events, including stroke.

2. Rheumatic heart disease. The incidence of focal cerebral ischemia is increased in patients with rheumatic heart disease – particularly those with mitral stenosis and atrial fibrillation – presumably as a result of embolization. In other cases, symptoms are temporally related to exertion, suggesting hypoperfusion as the cause.

3. Arrhythmias. Atrial fibrillation (especially when associated with rheumatic heart disease) and the bradycardia-tachycardia (sick-sinus) syndrome are well-recognized causes of embolic stroke. Other cardiac arrhythmias are

more likely to produce pancerebral hypoperfusion with diffuse rather than focal symptoms (eg, syncope, dimming of vision, nonspecific lightheadedness, generalized seizures) unless severe carotid artery stenosis is also present.

4. Endocarditis

a. Infective (bacterial or fungal) endocarditis is a cause of transient cerebral ischemia and embolic cerebral infarction during the active phase of infection and during the first few months following antibiotic cure. At autopsy, cerebral emboli are identified in 30% and systemic emboli in 60% of such patients. The middle cerebral artery is the most common site of cerebral embolization. Intracerebral or subarachnoid hemorrhage can also occur as a result of bleeding into an infarct or rupture of a mycotic aneurysm. Infective endocarditis is seen most often in intravenous drug users and patients with valvular heart disease or prosthetic valves. Streptococci and staphylococci are the most common causes, but gram-negative bacilli (eg, *Pseudomonas)* and fungi (especially *Candida* and *Aspergillus)* are also frequent pathogens in intravenous drug users and prosthetic valve recipients.

Signs of infective endocarditis include heart murmurs, petechiae, subungual splinter hemorrhages, retinal Roth's spots (red spots with white centers), Osier's nodes (painful red or purple digital nodules), Janeway's lesions (red macules on the palms or soles), and clubbing of the fingers or toes. The diagnosis is usually made by culturing the responsible organism from the blood. Treatment is with antibiotics; valve replacement is sometimes required. Anticoagulation should be avoided because of the risk of intracranial hemorrhage.

b. Nonbacterial (marantic) endocarditis is most frequent in patients with cancer and is responsible for the vast majority of ischemic strokes in this population. The tumors most often associated with this type of stroke are adenocarcinomas of the lung or gastrointestinal tract. Vegetations are present on the mitral or aortic valves; associated murmurs are rare. Identification of valvular vegetations by two-dimensional echocardiography may be diagnostic, but failure to demonstrate vegetations does not exclude the diagnosis. Anticoagulation with heparin may be useful in patients with treatable tumors or with other treatable causes of marantic endocarditis, such as sepsis.

5. Mitral valve prolapse. Buckling of the mitral valve due to stretching of the mitral annulus (mitral valve prolapse) is common, occurring in 4-8% of young adults, and usually produces no symptoms. However, in some cases it is associated with significant mitral regurgitation, infective endocarditis, cardiac arrhythmias, or cerebral ischemic events. Mitral valve prolapse may be seen in association with coronary artery disease, cardiomyopathy, atrial septal defect, or connective tissue diseases, or as a familial disorder with autosomal dominant inheritance, but is usually idiopathic. Auscultation of the heart classically reveals a midsystolic click, and a holo- or late systolic murmur, and M-mode echocardiography shows abnormal motion of the mitral valve, which results from stretching of the mitral annulus. While there appears to be a genuine association of mi-

tral valve prolapse with cerebral ischemia, the degree to which the disorder increases the risk of stroke is apparently small, and massive strokes related to mitral valve prolapse are rare.

6. Paradoxic embolus. Congenital cardiac anomalies associated with a pathologic communication between the right and left sides of the heart, such as atrial septal defect or patent foramen ovale, permit the passage of embolic material from the systemic venous circulation to the brain. Under these circumstances, venous thrombi can give rise to embolic stroke.

7. Atrial myxoma. This rare disorder can lead to either embolization (producing stroke) or cardiac outflow obstruction (producing syncope). Embolic events occur in one-fourth to one-half of patients with nonhereditary left atrial myxoma; some cases, however, are familial. Hemorrhagic strokes may occur. Diagnosis is by echocardiography.

8. Prosthetic heart valves. Patients with prosthetic heart valves are at particular risk for cerebral emboli and are generally treated with anticoagulants on a long-term basis.

C. Hematological Disorders

1. Thrombocytosis. Thrombocytosis occurs in myeloproliferative disorders, in other systemic malignant neoplastic diseases or infections, and following splenectomy. Thrombocytosis may predispose to focal cerebral ischemia, particularly when the platelet count exceeds 1,000,000/μL. While hyperaggregability of platelets has also been described in association with focal cerebral ischemia, it is uncertain whether this is primary and causal or a result of the cerebrovascular disorder.

2. Polycythemia. The occurrence of neurologic signs and symptoms in patients with polycythemia has long been recognized. In addition to nonspecific signs such as headache, dizziness, and blurred vision, patients may have focal neurological symptoms that often respond to venesection. Hematocrits above 46% may be associated with reduced cerebral blood flow, but there is a poor correlation between blood viscosity measured in vitro and the risk of stroke. This risk increases with hematocrits of more than 50%, however, and rises dramatically above 60%.

3. Sickle cell disease. Sickle cell (hemoglobin S) disease results from a single amino acid substitution (Glu-6-Val) in the hemoglobin beta locus on chromosome 11 (11p15.5) that results in an abnormal beta hemoglobin chain. Persons of African, especially West African, descent are most frequently affected. The mutation causes the sickle-shaped deformation of erythrocytes when the partial pressure of oxygen in blood is reduced, and produces hemolytic anemia and vascular occlusions, which may be extremely painful (sickle cell crises). Homozygotes are more severely affected than heterozygotes. The most frequent neurological complication is stroke, which characteristically affects the intracranial internal carotid or proximal middle or anterior cerebral artery. De-

tection of increased cerebral blood flow velocity by transcranial Doppler studies may help to identify individuals at increased risk for stroke. Therapies in clinical or experimental use include hydration and analgesia for painful crises, blood transfusion, hydroxyurea (which increases levels of fetal hemoglobin), and bone marrow or hematopoietic stem cell transplantation. In patients with sickle cell disease who must undergo angiography, the level of hemoglobin S should be reduced by exchange transfusion to less than 20%, since radiologic contrast media may induce sickling.

4. Leukocytosis. Transient cerebral ischemia has been reported in association with leukocytosis, usually in patients with leukemia and white blood cell counts in excess of 150,000/μL.

5. Hypercoagulable states. Hyperviscosity of the serum from paraproteinemia (especially macroglobulinemia) is an infrequent cause of focal cerebral ischemia. Stasis of blood in these conditions can lead to cerebral infarction or diffuse encephalopathy.

Many conditions, such as estrogen therapy or the use of oral contraceptives, postpartum and postoperative states, and cancer, are accompanied by coagulation abnormalities. Patients with such coagulopathies may exhibit symptoms of cerebral thrombosis or embolism.

Antiphospholipid antibodies, including lupus anticoagulants and anticardiolipin antibodies, may be associated with an increased incidence of ischemic stroke. The mechanism by which anti phospholipid antibodies promote thrombosis is uncertain.

Stroke has also been reported in patients with hereditary coagulopathies, including heparin cofactor II deficiency, protein C deficiency, defective release of plasminogen activator, and factor XII deficiency.

Pathology

A. Infarction in Major-Cerebral-Artery Distribution. On gross inspection at autopsy, a recent infarct is a swollen, softened area of brain that usually affects both gray and white matter. Microscopy shows acute ischemic changes in neurons (shrinkage, microvacuolization, dark staining), destruction of glial cells, necrosis of small blood vessels, disruption of nerve axons and myelin, and accumulation of interstitial fluid from vasogenic edema. In some cases, perivascular hemorrhages are observed in the infarcted area.

Cerebral infarcts are typically associated with cerebral edema, which is maximal during the first 4 or 5 days after onset. Most deaths that occur within 1 week after massive cerebral infarction are attributable to cerebral edema, with swelling of the affected hemisphere causing herniation of the ipsilateral cingulate gyrus across the midline beneath the free edge of the dural falx, followed by downward displacement of the brain through the tentorial incisure.

B. Lacunar Infarction. In contrast to infarcts associated with major cerebral blood vessels, smaller lacunar infarcts result from lipohyalinosis of small

resistance vessels, usually in patients with chronic hypertension. Lacunar infarcts – often multiple – are found in about 10% of brains at autopsy. The pathologic appearance is of small cavities ranging in size from 0.5 to 15 mm in diameter.

Clinicoanatomic Correlation

A rational clinical approach to cerebral ischemia depends on the ability to identify the neuroanatomic basis of clinical deficits.

A. Anterior Cerebral Artery

1. Anatomy. The anterior cerebral artery supplies the parasagittal cerebral cortex, which includes portions of motor and sensory cortex related to the contralateral leg and the so-called bladder inhibitory or micturition center.

2. Clinical syndrome of anterior cerebral artery occlusion. Anterior cerebral artery strokes are uncommon, perhaps because emboli from the extracranial vessels or the heart are more apt to enter the larger-caliber middle cerebral artery, which receives the bulk of cerebral blood flow. There is a contralateral paralysis and sensory loss affecting the leg. Voluntary control of micturition may be impaired because of failure to inhibit reflex bladder contractions, resulting in precipitate micturition.

B. Middle Cerebral Artery

1. Anatomy. The middle cerebral artery supplies most of the remainder of the cerebral hemisphere and deep subcortical structures. The cortical branches of the middle cerebral artery include the superior division, which supplies the entire motor and sensory cortical representation of the face, hand, and arm; and the expressive language (Broca's) area of the dominant hemisphere. The inferior division supplies the visual radiations, the region of visual cortex related to macular vision, and the receptive language (Wernicke's) area of the dominant hemisphere. Lenticulostriate branches of the most proximal portion (stem) of the middle cerebral artery supply the basal ganglia as well as motor fibers related to the face, hand, arm, and leg as they descend in the genu and the posterior limb of the internal capsule.

2. Clinical syndrome of middle cerebral artery occlusion. The middle cerebral artery is the vessel most commonly involved in ischemic stroke. Depending on the site of involvement, several clinical syndromes can occur.

a. Superior division stroke results in contralateral hemiparesis that affects the face, hand, and arm but spares the leg; contralateral hemisensory deficit in the same distribution; but no homonymous hemianopia. If the dominant hemisphere is involved, these features are combined with Broca's (expressive) aphasia, which is characterized by impairment of language expression with intact comprehension.

b. Inferior division stroke is less common in isolation and results in contralateral homonymous hemianopia that may be denser inferiorly; marked impairment of cortical sensory functions, such as graphesthesia and stereognosis

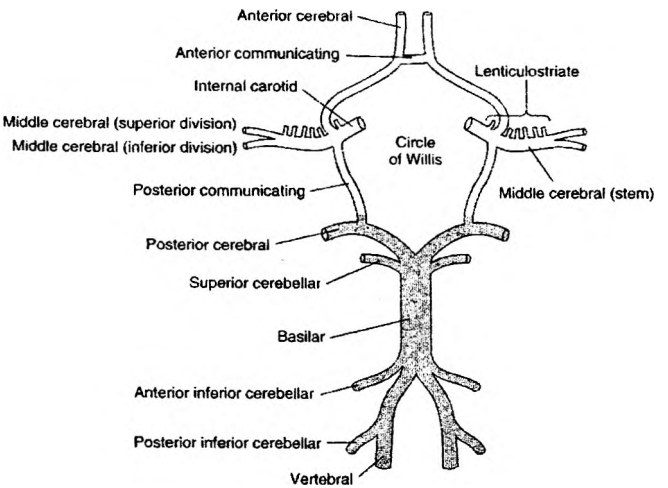
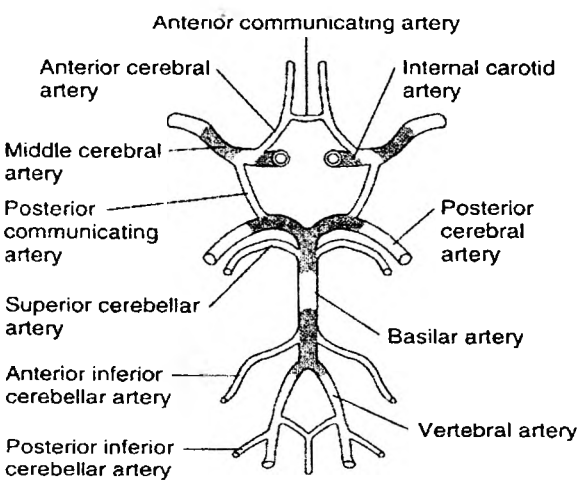


Fig. 14. Arteries of the anterior and posterior cerebral circulation in relation to the circle of Willis. Sites of predilection for atherosclerosis in the intracranial arterial circulation.



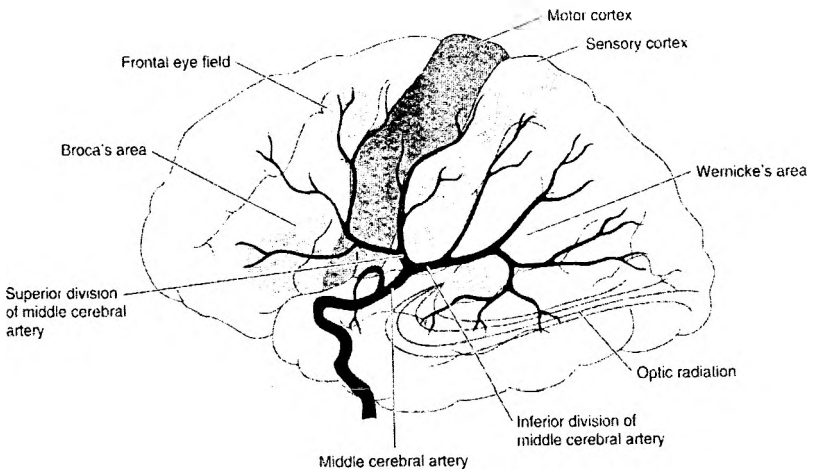


Fig. 15. Anatomic basis of middle cerebral artery syndromes.

on the contralateral side of the body; and disorders of spatial thought, including a lack of awareness that a deficit exists (anosognosia), neglect of and failure to recognize the contralateral limbs, neglect of the contralateral side of external space, dressing apraxia, and constructional apraxia. If the dominant hemisphere is involved, Wernicke's (receptive) aphasia occurs and is manifested by impaired comprehension and fluent but often nonsensical speech. With involvement of the nondominant hemisphere, an acute confusional state may occur.

c. Occlusion at the bifurcation or trifurcation of the middle cerebral artery involves a lesion situated at the point where the artery splits into two (superior and inferior) or three (superior, middle, and inferior) major divisions. This severe stroke syndrome combines the features of superior and inferior division stroke. Its clinical features include contralateral hemiparesis and hemisensory deficit involving the face and arm far more than the leg; homonymous hemianopia; and, if the dominant hemisphere is affected, global (combined expressive and receptive) aphasia.

d. Occlusion of the stem of the middle cerebral artery occurs proximal to the origin of the lenticulostriate branches. Since the entire territory of the artery is affected, this is the most devastating of middle cerebral artery strokes. The resulting clinical syndrome is similar to that seen following occlusion at the trifurcation except that, in addition, infarction of motor fibers in the internal capsule causes paralysis of the contralateral leg. The result is a contralateral hemiplegia and sensory loss affecting the face, hand, arm, and leg.

C. Internal Carotid Artery

1. Anatomy. The internal carotid artery arises where the common carotid artery divides into internal and external carotid branches in the neck. In addition to its anterior cerebral and middle cerebral branches discussed above, the internal carotid artery also gives rise to the ophthalmic artery, which supplies the retina. The severity of internal carotid artery strokes is highly variable, depending on the adequacy of collateral circulation, which tends to develop in compensation for a slowly evolving occlusion.

2. Clinical syndrome of internal carotid artery occlusion. Intra- or extracranial internal carotid artery occlusion is responsible for about one-fifth of ischemic strokes. In approximately 15% of cases, progressive atherosclerotic occlusion of the internal carotid artery is preceded by premonitory TIAs or by transient monocular blindness caused by ipsilateral retinal artery ischemia.

Carotid artery occlusion may be asymptomatic. Symptomatic occlusion results in a syndrome similar to that of middle cerebral artery stroke (contralateral hemiplegia, hemisensory deficit, and homonymous hemianopia; aphasia is also present with dominant hemisphere involvement).

D. Posterior Cerebral Artery

1. Anatomy. The paired posterior cerebral arteries arise from the tip of the basilar artery and supply the occipital cerebral cortex, medial temporal lobes, thalamus, and rostral midbrain. Emboli carried up the basilar artery tend to lodge

at its apex, where they can occlude one or both posterior cerebral arteries. These emboli can subsequently break up and produce signs of asymmetric or patchy posterior cerebral artery infarction.

2. Clinical syndrome of posterior cerebral artery occlusion. Occlusion of a posterior cerebral artery produces homonymous hemianopia affecting the contralateral visual field. Macular vision may be spared, however, because of the dual (middle and posterior cerebral artery) blood supply to the portion of the visual cortex representing the macula. In contrast to visual field defects from infarction in the middle cerebral artery territory, those caused by posterior cerebral artery occlusion may be denser superiorly. With occlusions near the origin of the posterior cerebral artery at the level of the midbrain, ocular abnormalities can include vertical gaze palsy, oculomotor (III) nerve palsy, internuclear ophthalmoplegia, and vertical skew deviation of the eyes. When posterior cerebral artery occlusion affects the occipital lobe of the dominant (usually left) hemisphere, patients may exhibit anomic aphasia (difficulty in naming objects), alexia without agraphia (inability to read, with no impairment of writing), or visual agnosia. The last is a failure to identify objects presented in the left side of the visual field, caused by a lesion of the corpus callosum that disconnects the right visual cortex from language areas of the left hemisphere. Bilateral posterior cerebral artery infarction may result in cortical blindness, memory impairment (from temporal lobe involvement), or the inability to recognize familiar faces (prosopagnosia), as well as a variety of exotic visual and behavioral syndromes.

E. Basilar Artery

1. Anatomy. The basilar artery usually arises from the junction of the paired vertebral arteries, though in some cases only a single vertebral artery is present. The basilar artery courses over the ventral surface of the brainstem to terminate at the level of the midbrain, where it bifurcates to form the posterior cerebral arteries (see above). Branches of the basilar artery supply the occipital and medial temporal lobes, the medial thalamus, the posterior limb of the internal capsule, and the entire brainstem and cerebellum.

2. Clinical syndromes of basilar artery occlusion.

a. Thrombosis. Thrombotic occlusion of the basilar artery – a serious event that is often incompatible with survival – produces bilateral neurologic signs referable to involvement of multiple branch arteries. Occlusion of both vertebral arteries or of a lone unpaired vertebral artery produces a similar syndrome. Temporary occlusion of one or both vertebral arteries can also occur in relation to rotation of the head in patients with cervical spondylosis, leading to transient symptoms and signs of brainstem dysfunction.

Major stenosis or occlusion of the subclavian artery before it has given rise to the vertebral artery can lead to the subclavian steal syndrome, in which blood passes from the vertebral artery into the distal subclavian artery with physical activity of the ipsilateral arm. The syndrome is a manifestation of generalized atherosclerosis and is not predictive of stroke in the vertebrobasilar sys-

tem. Patients are usually asymptomatic, and stroke, when it occurs, is typically due to coexisting carotid lesions.

Basilar thrombosis usually affects the proximal portion of the basilar artery, which supplies the pons. Involvement of the dorsal portion (tegmentum) of the pons produces unilateral or bilateral abducens (VI) nerve palsy; horizontal eye movements are impaired, but vertical nystagmus and ocular bobbing may be present. The pupils are constricted as a result of the involvement of descending sympathetic pupillodilator fibers in the pons, but they may remain reactive. Hemiplegia or quadriplegia is usually present, and coma is common. Although the syndrome of basilar occlusion in unconscious patients may be confused with pontine hemorrhage, a CT or MRI brain scan will differentiate the two.

In some patients with basilar occlusion, the ventral portion of the pons (basis pontis) is infarcted and the tegmentum is spared. Such patients remain conscious but quadriplegic. The term locked-in syndrome has been applied to this state. Locked-in patients may be able to signify that they are conscious by opening their eyes or moving their eyes vertically on command. In other cases, a conventional EEG with stimulation may be needed to distinguish the locked-in state (in which the EEG is normal) from coma.

b. Embolism. Emboli small enough to pass through the vertebral arteries into the larger basilar artery are usually arrested at the top of the basilar artery, where it bifurcates into the posterior cerebral arteries. The resulting reduction in blood flow to the ascending reticular formation of the midbrain and thalamus produces immediate loss or impairment of consciousness. Unilateral or bilateral oculomotor (III) nerve palsies are characteristic. Hemiplegia or quadriplegia with decerebrate or decorticate posturing occurs because of the involvement of the cerebral peduncles in the midbrain. Thus, the top of the basilar syndrome may be confused with midbrain failure caused by transtentorial uncal herniation. Less commonly, an embolus may lodge more proximally in an atheromatous narrowed portion of the basilar artery, producing a syndrome indistinguishable from basilar thrombosis.

Smaller emboli may occlude the rostral basilar artery transiently before fragmenting and passing into one or both posterior cerebral arteries. In such cases, portions of the midbrain, thalamus, and temporal and occipital lobes can be infarcted. If conscious, these patients display a variety of visual (homonymous hemianopia, cortical blindness), visuomotor (impaired convergence, paralysis of upward or downward gaze, diplopia), and behavioral (especially confusion) abnormalities without prominent motor dysfunction. Sluggish pupillary responses are a helpful sign of midbrain involvement.

F. Long Circumferential Vertebrobasilar Branches.

1. Anatomy. The long circumferential branches arising from the vertebral and basilar arteries are the posterior inferior cerebellar, the anterior inferior cerebellar, and the superior cerebellar arteries. These vessels supply the dorsolateral brainstem, including dorsolaterally situated cranial nerve nuclei (V, VII,

VIII) and pathways entering and leaving the cerebellum in the cerebellar peduncles.

2. Clinical syndrome of long circumferential artery occlusion. Occlusion of one of the circumferential branches produces infarction in the dorsolateral area of the medulla or pons.

a. Posterior inferior cerebellar artery occlusion results in the lateral medullary (Wallenberg's) syndrome. This syndrome varies in its presentation with the extent of infarction, but it can include ipsilateral cerebellar ataxia, Homer's syndrome, and facial sensory deficit; contralateral impaired pain and temperature sensation; and nystagmus, vertigo, nausea, vomiting, dysphagia, dysarthria, and hiccup. The motor system is characteristically spared because of its ventral location in the brain stem.

b. Anterior inferior cerebellar artery occlusion leads to infarction of the lateral portion of the caudal pons and produces a syndrome with many of the same features. Homer's syndrome, dysphagia, dysarthria, and hiccup do not occur, however, but ipsilateral facial weakness, gaze palsy, deafness, and tinnitus are common findings.

c. The syndrome of lateral rostral pontine infarction from **superior cerebellar artery occlusion** resembles that associated with anterior inferior cerebellar artery lesions, but impaired optokinetic nystagmus or skew deviation of the eyes may occur. Auditory function is unaffected, and the contralateral sensory disturbance may involve touch, vibration, and position sense as well as pain and temperature sense.

G. Long Penetrating Paramedian Vertebrobasilar Branches.

1. Anatomy. Long penetrating paramedian arteries supply the medial brainstem from its ventral surface to the floor of the fourth ventricle. Structures located in this region include the medial portion of the cerebral peduncle, sensory pathways, the red nucleus, the reticular formation, and the midline cranial nerve nuclei (III, IV, VI, XII).

2. Clinical syndrome of long penetrating paramedian artery occlusion. Occlusion of a long penetrating artery causes paramedian infarction of the brainstem and results in contralateral hemiparesis if the cerebral peduncle is affected. Associated cranial nerve involvement depends on the level of the brainstem at which occlusion occurs. Occlusion in the midbrain results in ipsilateral third nerve palsy, which may be associated with contralateral tremor or ataxia from involvement of pathways connecting the red nucleus and cerebellum. Ipsilateral 6th and 7th nerve palsies are seen in the pons, and 12th nerve involvement can occur in the medulla.

If the lesion appears patchy or involves both sides of the brainstem (as manifested by coma or quadriparesis), the differential diagnosis includes occlusion of a main trunk vessel (both vertebral arteries or the basilar artery); intramedullary lesions such as hemorrhage, pontine glioma, or multiple sclerosis;

and compression of the brainstem by a cerebellar mass (hemorrhage, infarct, or tumor).

H. Short Basal Vertebrobasilar Branches.

1. Anatomy. Short branches arising from the long circumferential arteries (discussed above) penetrate the ventral brainstem to supply the brainstem motor pathways.

2. Clinical syndrome of basal brainstem infarction. The most striking finding is contralateral hemiparesis caused by corticospinal tract involvement in the cerebral peduncle or basis pontis. Cranial nerves (eg, III, VI, VII) that emerge from the ventral surface of the brainstem may be affected as well, giving rise to ipsilateral cranial nerve palsies.

I. Lacunar Infarction. Small penetrating arteries located deep in the brain may become occluded as a result of changes in the vessel wall induced by chronic hypertension. The resulting lacunar infarcts are most common in deep nuclei of the brain (putamen, 37%; thalamus, 14%; caudate nucleus, 10%), the pons (16%), and the posterior limb of the internal capsule (10%). They occur in lesser numbers in the deep cerebral white matter, the anterior limb of the internal capsule, and the cerebellum. Because of their small size and their frequent location in relatively silent areas of the brain, many lacunar infarctions are not recognized clinically. In as many as three-fourths of autopsy-proved cases, there is no history of stroke or clear evidence of neurologic deficit on antemortem examinations.

In many cases, the isolated nature of the neurologic deficit makes the clinical picture of lacunar infarction distinctive. The onset of lacunar stroke may be gradual, developing over several hours or days. Headache is absent or minor, and the level of consciousness is unchanged.

Recognition of lacunar stroke syndromes is important because the prognosis for complete or nearly complete recovery is good. In addition, the likelihood of future lacunar strokes can be reduced by treating the hypertension that is usually associated with and causally related to them. Because the arteries involved are small, angiography is normal (for that reason, it is not required). The CSF is also normal, and it is possible that a CT brain scan or MRI will not disclose the lesion. CT scanning or MRI should be performed to exclude other causes of stroke, however. Anticoagulation is not indicated since there is no evidence that it confers any benefit in this context. Aspirin is also of uncertain benefit, but it is often given because of the low risk of serious complications. Although a wide variety of deficits can be produced, there are four classic and distinctive lacunar syndromes.

1. Pure motor hemiparesis. This consists of hemiparesis affecting the face, arm, and leg to a roughly equal extent, without an associated disturbance of sensation, vision, or language. When lacunar in origin, it is usually due to a lesion in the contralateral internal capsule or pons. Pure motor hemiparesis may

also be caused by internal carotid or middle cerebral artery occlusion, subdural hematoma, or intracerebral mass lesions.

2. Pure sensory stroke. This is characterized by hemisensory loss, which may be associated with paresthesia, and results from lacunar infarction in the contralateral thalamus. It may be mimicked by occlusion of the posterior cerebral artery or by a small hemorrhage in the thalamus or midbrain.

3. Ataxic hemiparesis. In this syndrome (sometimes called ipsilateral ataxia and crural (leg) paresis), pure motor hemiparesis is combined with ataxia of the hemiparetic side and usually predominantly affects the leg. Symptoms result from a lesion in the contralateral pons, internal capsule, or subcortical white matter.

4. Dysarthria – clumsy hand syndrome. This consists of dysarthria, facial weakness, dysphagia, and mild weakness and clumsiness of the hand on the side of facial involvement. When the syndrome is caused by a lacunar infarct, the lesion is in the contralateral pons or internal capsule. Infarcts or small intracerebral hemorrhages at a variety of locations can produce a similar syndrome, however. In contrast to the lacunar syndromes described above, premonitory TIAs are unusual.

Clinical Findings

A. History

1. Predisposing factors. In patients with cerebrovascular disorders, possible risk factors such as TIAs, hypertension, and diabetes should be sought. In women, the use of oral contraceptives has been associated with cerebral arterial and venous occlusive disease, especially in the presence of hypertension and cigarette smoking. The presence of such medical conditions as ischemic or valvular heart disease or cardiac arrhythmias must also be ascertained. A variety of systemic disorders involving the blood or blood vessels also increase the risk of stroke. Antihypertensive drugs can precipitate cerebrovascular symptoms if the blood pressure is lowered excessively in patients with nearly total cerebrovascular occlusion and poor collateral circulation.

2. Onset and course. The history must address whether the clinical picture is that of TIA, stroke in evolution, or completed stroke. In some cases, it may also be possible to evaluate whether a stroke is likely to be thrombotic or embolic in origin from the clinical history.

a. Features suggesting thrombotic stroke. Patients with thrombotic vascular occlusion often present with stepwise incremental neurologic deficits; the occlusion may be preceded by a series of TIAs. TIAs, for example, precede infarction in 25-50% of patients with occlusive atherosclerotic disease of the extracranial internal carotid arteries. In approximately one-third of such patients,

however, the onset of infarction is abrupt, suggesting that embolization from the distal extracranial artery to the intracranial artery may be the cause of stroke.

b. Features suggesting embolic stroke. Cerebral embolism typically causes neurologic deficits that occur abruptly with no warning and are maximal at onset. In many patients, a cardiac origin of emboli is suggested by signs of multifocal cerebral infarction, cardiac valvular disease, cardiomegaly, arrhythmias, or endocarditis.

3. Associated symptoms

a. Seizures accompany the onset of stroke in a small number of cases; in other instances, they follow the stroke by weeks to years. The presence of seizures does not definitively distinguish embolic from thrombotic strokes, but seizure at the onset of stroke may be more common with embolus. If patients with vertebrobasilat stroke or an additional condition predisposing to seizures are not considered, the incidence of epilepsy after stroke is about 10%. The risk of epilepsy increases to about 25% with cortical strokes and to 50% when cortical strokes are associated with a persistent motor deficit.

b. Headache occurs in about 25% of patients with ischemic stroke, possibly because of the acute dilation of collateral vessels.

B. Physical Examination

1. General physical examination. The general physical examination of a patient with a cerebrovascular disorder should focus on searching for an underlying systemic cause, especially a treatable one.

a. The blood pressure should be measured to ascertain whether hypertension – a known risk factor for stroke – is present.

b. Comparison of blood pressure and pulse on the two sides can reveal differences related to atherosclerotic disease of the aortic arch or coarctation of the aorta.

c. Ophthalmoscopic examination of the retina can provide evidence of embolization in the anterior circulation in the form of visible embolic material in retinal blood vessels.

d. Examination of the neck may reveal the absence of carotid pulses or the presence of carotid bruits. Reduced carotid artery pulsation in the neck is a poor indicator of internal carotid artery disease, however. Although carotid bruits have been associated with cerebrovascular disease, significant carotid stenosis can occur without an audible bruit; conversely, a loud bruit can occur without stenosis.

e. A careful cardiac examination is essential in order to detect arrhythmias or murmurs related to valvular disease, either of which may predispose to embolization from heart to brain.

f. Palpation of the temporal arteries is useful in the diagnosis of giant cell arteritis, in which these vessels may be tender, nodular, or pulseless.

2. Neurologic examination. Patients with cerebrovascular disorders mayor may not have abnormal neurologic findings on examination. A normal

examination is expected, for example, after a TIA has resolved. Where deficits are found, the goal of the neurologic examination is to define the anatomic site of the lesion, which may suggest the cause or optimal management of the stroke. Thus, clear evidence that the anterior circulation is involved may lead to angiographic evaluation in contemplation of possible surgical correction of an internal carotid lesion. Establishing that the symptoms are referable to the vertebrobasilar circulation or to a lacunar infarction is likely to dictate a different course of action.

a. Cognitive deficits that indicate cortical lesions in the anterior circulation should be sought. For example, if aphasia is present, the underlying disorder cannot be in the posterior circulation and is unlikely to represent lacunar infarction. The same is true for nondominant hemisphere lesions producing parietal lobe syndromes such as unilateral neglect or constructional apraxia (see discussion of inferior division middle cerebral artery stroke, above).

b. The presence of visual field abnormalities similarly excludes lacunar infarction. Hemianopia may occur, however, with involvement of either the anterior or posterior cerebral arteries. Isolated hemianopia suggests posterior cerebral artery infarction.

c. Ocular palsies, nystagmus, or internuclear ophthalmoplegia assign the underlying lesion to the brainstem and thus to the posterior circulation.

d. Hemiparesis can be due to lesions in cerebral cortical regions supplied by the anterior circulation, descending motor pathways in the brainstem supplied by the vertebrobasilar system, or lacunae at subcortical (corona radiata, internal capsule) or brainstem sites. However, hemiparesis affecting the face, hand, and arm more than the leg is characteristic of lesions within the distribution of the middle cerebral artery. Hemiparesis that is nonselective with respect to the face, arm, and leg is consistent with occlusion of the internal carotid artery or the stem of the middle cerebral artery, lacunar infarction in the internal capsule or basal ganglia, or brainstem disease. A crossed hemiparesis – ie, one that involves the face on one side and the rest of the body on the other – means that the abnormality must lie between the level of the facial nerve nucleus in the pons and the decussation of the pyramids in the medulla.

e. Cortical sensory deficits such as astereognosis and agraphesthesia with preserved primary sensory modalities imply a cerebral cortical deficit within the territory of the middle cerebral artery. Isolated hemisensory deficits without associated motor involvement are usually lacunar in origin. Crossed sensory deficits result from brainstem lesions in the medulla, as seen in the lateral medullary plate syndrome.

f. Hemiataxia usually points to a lesion in the ipsilateral brainstem or cerebellum but can also be produced by lacunae in the internal capsule.

Investigative Studies

A. Blood Tests. These should be obtained routinely to detect treatable causes of stroke and to exclude conditions that can mimic stroke. The recommended studies are listed below.

1. Complete blood count to investigate such possible causes of stroke as thrombocytosis, thrombocytopenia, polycythemia, anemia (including sickle cell disease), and leukocytosis (eg, leukemia).

2. Erythrocyte sedimentation rate to detect elevations indicative of giant cell arteritis or other vasculitides.

3. Serologic assay for syphilis – treponemal assay in blood, such as the FTA-ABS or MHA-TP, or the CSF VDRL test.

4. Serum glucose to document hypoglycemia or hyperosmolar nonketotic hyperglycemia, which can present with focal neurologic signs and thereby masquerade as stroke.

5. Serum cholesterol and lipids to detect elevations that can represent risk factors for stroke.

B. ECG. An ECG should be obtained routinely to detect unrecognized myocardial infarction or cardiac arrythmias, such as atrial fibrillation, which predispose to embolic stroke.

C. CT Scan or MRI. A CT scan or MRI should be obtained routinely to distinguish between infarction and hemorrhage as the cause of stroke, to exclude other lesions (eg, tumor, abscess) that can mimic stroke, and to localize the lesion. CT is usually preferred for initial diagnosis because it is widely available and rapid and can readily make the critical distinction between ischemia and hemorrhage. MRI may be superior to CT scan for demonstrating early ischemic infarcts, showing ischemic strokes in the brainstem or cerebellum, and detecting thrombotic occlusion of venous sinuses.

D. Lumbar Puncture. This should be performed in selected cases to exclude subarachnoid hemorrhage (manifested by xanthochromia and red blood cells) or to document meningovascular syphilis (reactive VDRL) as the cause of stroke.

E. Cerebral Angiography. Inta-arterial angiography is used to identify operable extracranial carotid lesions in patients with anterior circulation TIAs who are good surgical candidates. It is also useful in the diagnosis of certain vascular disorders associated with stroke, including vasculitis, fibromuscular dysplasia, and carotid or vertebral artery dissection. Transfemoral arch aortography with selective catheterization of the carotid (and, if indicated, vertebral) arteries is the procedure of choice. Magnetic resonance angiography may detect stenosis of large cerebral arteries, aneurysms, and other vascular lesions, but its sensitivity is generally inferior to that of conventional angiography.

F. Ultrasonography. Doppler ultrasonography can detect stenosis or occlusion of the internal carotid artery, but it lacks the sensitivity of angiography.

In cases where the likelihood of finding operable symptomatic carotid stenosis is insufficient to justify the risk of angiography or where the risk is especially high because of coexisting illness or the lack of angiographic expertise, the finding of normal carotid blood flow or complete occlusion by Doppler studies can obviate the need for angiography. Transcranial doppler ultrasonography is sometimes used in the evaluation of suspected stenosis of the intracranial internal carotid artery, middle cerebral artery, or basilar artery and for detecting and following the course of cerebral vasospasm after aneurysmal subarachnoid hemorrhage.

G. Echocardiography. Echocardiography may be useful for demonstrating the cardiac lesions responsible for embolic stroke in patients' with clinically evident cardiac disease, such as atrial fibrillation.

H. EEG. The EEG is rarely useful in evaluating stroke. It may, however, help differentiate between a seizure disorder and TIAs or between lacunar and cortical infarcts in the occasional patient in whom these possibilities cannot otherwise be distinguished.

Differential Diagnosis

In patients presenting with focal central nervous system dysfunction of sudden onset, ischemic stroke must be distinguished from structural and metabolic processes that can mimic it. An underlying process other than focal cerebral ischemia should be suspected when the resulting neurologic deficit does not conform to the distribution of any single cerebral artery. In addition, strokes do not typically impair consciousness in the absence of profound focal deficits, while other cerebral disorders may do so.

Vascular disorders mistaken for ischemic stroke include intracerebral hemorrhage, subdural or epidural hematoma, and subarachnoid hemorrhage from rupture of an aneurysm or vascular malformation. These conditions can often be distinguished by a history of trauma or of excruciating headache at onset, a more marked depression of consciousness, or by the presence of neck stiffness on examination. They can be excluded by CT scan or MRI.

Other structural brain lesions such as tumor or abscess can also produce focal cerebral symptoms of acute onset. Brain abscess is suggested by concurrent fever, and both abscess and tumor can usually be diagnosed by CT scan or MRI. Metabolic disturbances, particularly hypoglycemia and hyperosmolar nonketotic hyperglycemia, may present in strokelike fashion. The serum glucose level should therefore be determined in all patients with apparent stroke.

Treatment

A. Asymptomatic Carotid Bruit or Stenosis. Carotid bruits are commonly detected during routine examinations of asymptomatic patients, with a frequency that reaches 7% above age 65. Carotid artery stenosis is also common,

and can be demonstrated by ultrasonography in as many as 30% of men over age 75. Because the natural history of carotid artery stenosis is variable, the relationship of asymptomatic bruit or stenosis to an individual's risk for stroke is difficult to assess. In large studies, severe stenosis is associated with increased stroke risk (2.5% per year for ipsilateral stroke with 75% stenosis), but the risk of contralateral stroke is increased as well, and the risk of myocardial ischemia in these patients is even higher. Moreover, carotid endarterectomy – which has been advocated in this setting – carries significant perioperative risk of stroke or death, and this risk varies widely across institutions. Although asymptomatic patients with high-grade carotid stenosis have appeared to benefit from endarterectomy in some studies, this effect was dependent on an extremely low surgical morbidity and mortality rate. For these reasons, antiplatelet therapy with aspirin (see below) is probably the approach of choice for asymptomatic carotid bruit or stenosis at present.

B. Transient Ischemic Attack. Because TIAs can indicate an impending stroke and because it may be possible to prevent such an event by appropriate treatment, TIAs must be accurately and promptly diagnosed and treatment instituted.

1. Antiplatelet therapy. Of the various medical treatments proposed for stroke prophylaxis in patients with noncardiogenic TIAs, antiplatelet agents appear to have the best benefit-to-risk ratio. The rationale for this approach is that embolism from platelet-fibrin thrombi on arterial surfaces may be responsible for many cases of TIA and stroke. Antiplatelet agents interfere with platelet function by irreversibly inhibiting the enzyme cyclooxygenase-I, which catalyzes the synthesis of thromboxane A_2 an eicosanoid with procoagulant and platelet-aggregating properties.

Aspirin, when administered to patients with TIAs or minor stroke (defined as little or no neurologic deficit after 1 week), has been shown to reduce the incidence of subsequent TIAs, stroke, or death in several studies. Although most studies have focused on noncardiogenic TIA or stroke, aspirin is also beneficial for preventing recurrent cerebral ischemia caused by cardiac emboli. In some cases (eg, patients with artificial heart valves), the combination of aspirin and anticoagulation may be more effective than anticoagulation alone. Doses of aspirin between 80 and 1300 mg orally daily (one baby aspirin to four adult aspirin tablets) appear to be effective, and daily oral administration of 325 mg of aspirin is probably used most often in North America. A sex-related difference in benefit favoring men has been observed, but only inconsistently. Administration of low-dose aspirin (325 mg orally every other day) to men age 40 and older without a history of TIA or stroke does not reduce the risk of stroke, although it decreases the incidence of myocardial infarction. Adverse effects of aspirin include dyspepsia, nausea, abdominal pain, diarrhea, skin rash, peptic ulcer, gastritis, and gastrointestinal bleeding.

Ticlopidine (250 mg orally twice daily), another antiplatelet agent, may be somewhat more effective than aspirin in preventing stroke and reducing mortality in patients with TIAs or mild stroke. However, ticlopidine is more expensive than aspirin and appears to be associated with such side effects as diarrhea, skin rash, and occasional cases of severe but reversible neutropenia.

Clopidogrel (75 mg orally daily), which inhibits platelet aggregation by binding irreversibly to adenosine diphosphate (ADP) receptors on the platelet surface, has also been shown to reduce the incidence of ischemic stroke, myocardial infarction, or death from other vascular causes in patients with recent ischemic stroke, myocardial infarction, or symptomatic peripheral arterial disease. Diarrhea and skin rash were more common than with aspirin, but neutropenia and thrombocytopenia occurred at the same rate.

Other antiplatelet drugs such as sulfinpyrazone and dipyridamole are commonly used to treat thrombotic vascular disease. Some evidence indicates that the combination of aspirin (25 mg) and extended-release dipyridamole (200 mg), taken orally twice daily, reduces the risk of stroke in patients with prior TIA or stroke to a greater extent than aspirin alone. Glycoprotein IIb/IIIa antagonists are also under investigation as platelet aggregation inhibitors.

2. Anticoagulation. Anticoagulation is indicated for patients with TIAs caused by cardiac embolus and is typically continued indefinitely or for as long as the cause of embolization (eg, atrial fibrillation or prosthetic heart valve) persists. The value of anticoagulation for TIAs from arterial thrombosis is uncertain.

Heparin is the drug of choice for acute anticoagulation, while warfarin is used for long-term therapy. Heparin is usually administered by continuous intravenous infusion at 1000-2000 units/h. The activated partial thromboplastin time (aPTT) is measured at least daily, and the dose of heparin is adjusted to maintain the aPTT at about 1.5 to 2.5 times the pretreatment value.

Warfarin (the usual maintenance dose is 5-15 mg/d orally) can be started simultaneously with heparin therapy. About 2 days after the prothrombin time (PT) reaches roughly one and one-half times the pretreatment value (typically about 5 days), heparin can be discontinued. The PT or international normalized ratio (INR) should be measured at least every 2 weeks and the dose of warfarin adjusted to maintain PT = 1.5 times control or INR = 3.0-4.0.

Enthusiasm for the use of anticoagulant therapy should be tempered by an appreciation of its potential hazards. The risk of intracranial hemorrhage is greatest in hypertensive patients and those over 65 years of age.

3. Carotid endarterectomy. Carotid endarterectomy involves the surgical removal of thrombus from a stenotic common or internal carotid artery in the neck. In patients with anterior-circulation TIAs and moderate (50-70%) or high-grade (70-99%) carotid stenosis on the side appropriate to account for the symptoms, the combination of endarterectomy and aspirin is superior to aspirin alone for preventing stroke. Endarterectomy has no place in the treatment of vertebro-

basilar TIAs or those related to intracranial arterial disease or complete carotid occlusion. The value of carotid endarterectomy for minimally stenotic but ulcerated carotid lesions is uncertain. The operative mortality rate for carotid endarterectomy has ranged from 1 to 5% or more.

4. Intralumenal stents. Surgical placement of tubular metal stents to maintain lumen patency in stenotic cerebral arteries is under investigation.

5. Extracranial-intracranial bypass. Many patients with TIAs referable to the carotid circulation have stenoses in intracranial portions of the artery not accessible through the neck, or they exhibit tandem lesions in both the extracranial and intracranial cerebral circulations. Because carotid endarterectomy does not correct these problems, an alternative approach has been explored involving anastomosis of the extracranial (temporal artery) and intracranial (middle cerebral artery) circulations distal to the stenosis. The bulk of current evidence suggests that this bypass procedure is ineffective.

6. Conclusions. In experienced hands, carotid endarterectomy can be a safe procedure that reduces the risk of subsequent TIAs or stroke in patients with carotid TIAs. Angiography should be used with these patients to define surgically accessible moderate to high-grade (50-99%) stenotic lesions.

Medical treatment with aspirin should be instituted with both nonsurgical and postoperative patients. For patients who continue to have TIAs despite aspirin treatment, increasing the dose of aspirin, substituting ticlopidine or clopidogrel, or adding sulfinpyrazone or dipyridamole should be considered. Alternatively, a 3-month course of warfarin should be substituted unless there are contraindications such as active peptic ulcer disease or severe hypertension. The prothrombin time should be maintained at one and one-half times the control value (INR = 3.0-4.0). In addition to the above measures, such contributory risk factors as hypertension and cardiac disease should be treated and cigarette smoking discontinued.

C. Stroke in Evolution. The optimal treatment for stroke in evolution is uncertain. The onset of aspirin's antiplatelet effect is delayed after oral administration, and endarterectomy also involves considerable delay in treatment.

The most widely used treatment is anticoagulation with heparin and subsequent administration of warfarin at the doses described above, although the efficacy of this approach has not been proved.

Thrombolytic agents such as tissue plasminogen activator might also be of value for stroke in evolution, but require further study in this context.

D. Completed Stroke

1. Thrombolytic agents. Tissue plasminogen activator (t-PA) is a serine protease that maps to chromosome 8 (8p12) in humans and catalyzes the conversion of plasminogen to plasmin. This accounts for its ability to lyse fibrin-containing clots such as those found in cerebrovascular thrombotic lesions. Some but not all controlled clinical data suggest that the intravenous administration of recombinant t-PA (rt-PA) within 3 hours of the onset of symptoms re-

duces disability and mortality from ischemic stroke (technically, from TIA, since stroke is defined by a deficit that persists for at least 24 hours). The drug is administered at a dose of 0.9 mg/kg, up to a maximum total dose of 90 mg; 10% of the dose is given as an intravenous bolus and the remainder as a continuous intravenous infusion over 60 minutes. The efficacy of rt-PA given more than 3 hours after symptoms begin, of other thrombolytic agents such as urokinase, or of intra-arterial administration of these agents has not been demonstrated in stroke.

The major complication of rt-PA treatment is hemorrhage, which may affect the brain or other tissues. The lack of proven benefit when rt-PA is given after 3 hours, the risk of bleeding complications, and the importance of a correct diagnosis when treatment is potentially dangerous dictate that rt-PA not be given in certain settings. It is important that the time of onset of symptoms can be established with confidence. The CT scan should not already show evidence of a large ischemic stroke or of hemorrhage. Patients whose coagulation function has been compromised by the administration of warfarin or heparin or by thrombocytopenia (platelet count <100,000/mm3) should not receive rt-PA, nor should those who are at increased risk of hemorrhage because of seizures at the onset of symptoms, prior intracranial hemorrhage, another intracranial disorder (including stroke or trauma) within 3 months, a major surgical procedure within 14 days, bleeding from the gastrointestinal or urinary tract within 21 days, or marked hypertension (systolic blood pressure >185 mm Hg or diastolic blood pressure >110 mm Hg). To avoid treating TIAs that are already resolving or other conditions unlikely to respond to rt-PA, or for which the risk exceeds likely benefit, patients whose deficits are improving rapidly and spontaneously, patients with mild and isolated deficits, and those with blood glucose concentrations consistent with a hypo- or hypergycemic origin of symptoms <50 mg/dl or >400 mg/dl) should be excluded.

Patients receiving rt-PA for stroke should be managed in facilities where the capacity exists to diagnose stroke with a high degree of certainty and to manage bleeding complications. Within the first 24 hours after administration of rt-PA, anticoagulants and antiplatelet agents should not be given, blood pressure should be carefully monitored, and arterial puncture and placement of central venous lines, bladder catheters, and nasogastric tubes should be avoided.

2. Antiplatelet agents. As noted above in discussing the treatment of TIAs, some but not all studies have shown a decrease in the incidence of subsequent stroke when aspirin is administered chronically following a stroke. The regimen is as described in the section on treatment of TIA.

3. Anticoagulation. Anticoagulation has not been shown to be useful in most cases of completed stroke. An exception is where a persistent source of cardiac embolus is present; anticoagulation is then indicated to prevent subsequent embolic strokes, although it does not affect the course of the stroke that has already occurred. Recent evidence indicates that while immediate anticoagu-

lation of such patients may result in hemorrhage into the infarct, this rarely affects the ultimate outcome adversely unless the infarct is massive. The risk of hemorrhage is more than offset by the particularly high risk of recurrent embolization soon after an embolic stroke, and anticoagulation should not be delayed in this setting. Heparin and warfarin are administered as described in the section on treatment of TIA.

4. Surgery. The indications for surgical treatment of completed stroke are extremely limited. When patients deteriorate as a consequence of brainstem compression following cerebellar infarction, however, posterior fossa decompression with evacuation of infarcted cerebellar tissue can be lifesaving.

5. Antihypertensive agents. Although hypertension contributes to the pathogenesis of stroke and many patients with acute stroke have elevated blood pressures, attempts to reduce the blood pressure in stroke patients can have disastrous results, since the blood supply to ischemic but as yet uninfarcted brain tissue may be further compromised. Therefore, such attempts should not be made. In the usual course of events, the blood pressure declines spontaneously over a period of hours to a few days.

6. Antiedema agents. Antiedema agents such as mannitol and corticosteroids have not been shown to be of benefit for cytotoxic edema (cellular swelling) associated with cerebral infarction.

7. Neuroprotective agents. A variety of drugs with diverse pharmacologic actions have been proposed as neuroprotective agents that might reduce ischemic brain injury by decreasing cerebral metabolism or interfering with the cytotoxic mechanisms triggered by ischemia. These include barbiturates and the opioid antagonist naloxone, neither of which appears to be beneficial in stroke.

Drugs that block voltage-gated or excitatory amino acid receptor-gated calcium channels have potential value in the treatment of stroke because cellular calcium overload may be an important mediator of irreversible ischemic neuronal injury. Clinical trials with these and related agents have yielded disappointing results thus far, however.

Prognosis

Outcome following stroke is influenced by a number of factors, the most important being the nature and severity of the resulting neurologic deficit. The patient's age, the cause of stroke, and coexisting medical disorders also affect prognosis. Overall, somewhat less than 80% of patients with stroke survive for at least 1 month, and 10-year survival rates in the neighborhood of 35% have been cited. The latter figure is not surprising, considering the advanced age at which stroke commonly occurs. Of patients who survive the acute period, about one-half to two-thirds regain independent function, while approximately 15% require institutional care.

GLOBAL CEREBRAL ISCHEMIA

Etiology

Global cerebral ischemia occurs when the blood flow is inadequate to meet the metabolic requirements of the brain, as in cardiac arrest. The result is a spectrum of neurologic disorders. The greater severity of neurologic involvement in ischemia than in pure anoxia may be due to the fact that in the former condition, the delivery of glucose and removal of potentially toxic metabolites are also impaired.

Pathology

Neuropathologic changes depend on the degree and duration of cerebral ischemia.

A. Distribution. Complete interruption of cerebral blood flow followed by reperfusion, such as occurs in cardiac arrest with resuscitation, produces damage that selectively affects metabolically vulnerable neurons of the cerebral cortex, basal ganglia, and cerebellum.

With less profound hypotension for prolonged periods, the damage is concentrated in the anatomically vulnerable border zones between the territories supplied by the major arteries of cerebral cortex, cerebellum, basal ganglia, and spinal cord. It is most severe in the watershed region between the territories supplied by the anterior, middle, and posterior cerebral arteries.

B. Modifying Factors. Reducing cerebral energy requirements, such as with deep anesthesia or hypothermia, can minimize or prevent brain damage from ischemic insults. Hyperglycemia or hypermetabolic states such as status epilepticus, on the other hand, can increase ischemic damage. Superimposed occlusive atherosclerotic disease of the craniocervical arteries may lead to asymmetries in the distribution of cerebral damage from panhypoperfusion.

Clinical Findings

A. Brief Ischemic Episodes. Reversible encephalopathies are common following brief episodes of systemic circulatory arrest. In such cases, coma persists for less than 12 hours. Transient confusion or amnesia may occur on awakening, but recovery is rapid and complete. Some patients show a severe anterograde and variable retrograde amnesia and a bland, unconcerned affect with or without confabulation. Recovery often occurs within 7-10 days but may be delayed by 1 month or longer. This syndrome may reflect reversible bilateral damage to the thalamus or hippocampus.

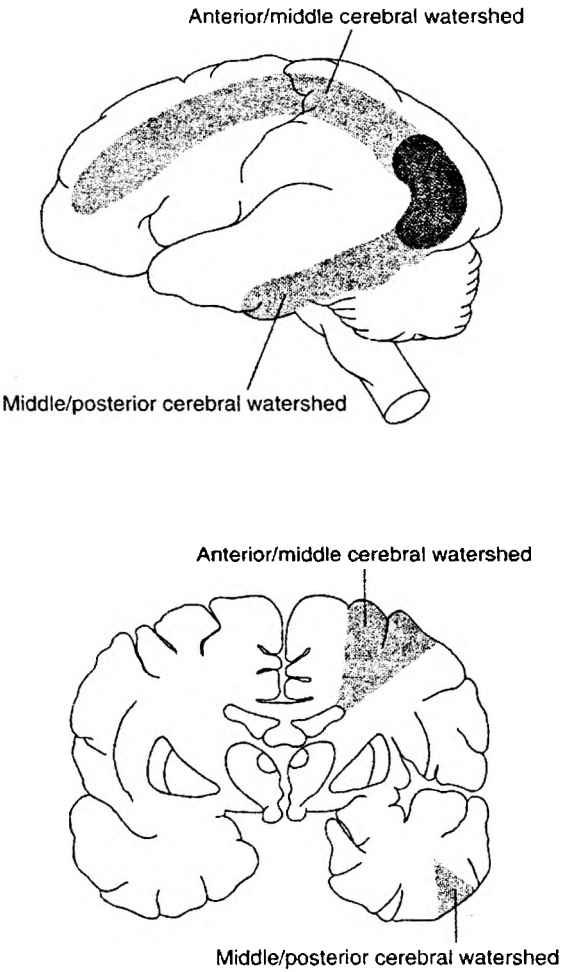


Fig. 16. Distribution of watershed cerebral infarctions.

B. Prolonged Ischemic Episodes

1. Focal cerebral dysfunction. Patients are usually comatose for at least 12 hours and may have lasting focal or multifocal motor, sensory, and cognitive deficits if they awaken. Full recovery may not occur or may require weeks to months. Some such patients are eventually capable of leading an independent existence, while those who are more severely disabled may require institutional care.

Focal neurologic signs after cardiac arrest include partial or complete cortical blindness, weakness of both arms (bibrachial paresis), and quadriparesis. Cortical blindness is usually transient but can rarely be permanent. It probably results from disproportionate ischemia of the occipital poles because of their location in the border zone between the middle and posterior cerebral arteries. Bibrachial paresis (man-in-a-barrel syndrome) results from bilateral infarction of the motor cortex in the border zone between the anterior and middle cerebral arteries.

2. Persistent vegetative state. Some patients who are initially comatose following cardiac arrest survive and awaken but remain functionally decorticate and unaware of their surroundings. They typically regain spontaneous eye-opening, sleep-wake cycles, and roving eye movements and brainstem and spinal cord reflexes. The persistent vegetative state is thus distinct from coma and appears to be associated with destruction of the neocortex. A persistent vegetative state associated with an isoelectric (flat) EEG is termed neocortical death. Persistent vegetative states must be distinguished from brain death, in which both cerebral and brainstem function are absent.

3. Spinal cord syndromes. The spinal cord seems to be more resistant to transient ischemia than the brain, so that cord damage from hypoperfusion is usually accompanied by profound cerebral involvement. Hypoperfusion does occasionally lead to isolated spinal cord infarction, however. In such cases, the anterior and central structures of the spinal cord are more involved because of their location in the critical border zones between territories supplied by the anterior and posterior spinal arteries. These watersheds, especially in the upper and lower levels of the thoracic cord, are vulnerable to profound drops in perfusion pressure. In the acute period, spinal stroke from hypotension produces a flaccid paraplegia and urinary retention. The sensory level in the thoracic region is characterized more by marked impairment of pain and temperature sensation than of light touch. With time, flaccid paralysis is replaced by spastic paraplegia with brisk tendon reflexes in the legs and extensor plantar responses.

Treatment

A. Established Measures. The clinical management of patients in coma caused by global cerebral ischemia involves immediate restoration of adequate cerebral circulation, elimination of cardiac dysrhythmias, maintenance of effective systemic blood pressure, and correction of acid-base or electrolyte abnor-

malities. Ventilatory assistance may be necessary if either medullary depression or injury to the chest wall prevents adequate ventilation, and supplemental oxygen can also be administered.

Beyond these measures, there are no other uniformly satisfactory methods of treatment. Attempts to prevent cerebral edema in this setting have not been successful, and treatment with corticosteroids, dehydrating agents, calcium channel antagonists, hypothermia, and hyperventilation have not improved the prognosis.

B. Experimental Measures. Although barbiturates have a protective effect in some experimental models of global cerebral ischemia, a similar benefit does not appear to occur in patients.

Excitatory amino acid receptor antagonists may find application in the treatment of cerebral anoxic ischemia but are at present experimental. The rationale for considering the use of these drugs lies in existing evidence that ischemia or hypoxia may trigger the release of excitatory amino acid neurotransmitters, which may in turn interact with vulnerable neurons to promote cell death.

INTRACEREBRAL HEMORRHAGE

Hypertensive Hemorrhage

Hypertension is the most common underlying cause of nontraumatic intracerebral hemorrhage.

A. Pathophysiology

1. Cerebral autoregulation. Autoregulation of cerebral blood flow, which is achieved by changes in the caliber of small resistance cerebral arteries, maintains constant cerebral blood flow as systemic blood pressure rises and falls. The range of autoregulated blood pressures is variable.

In normotensive individuals, the lowest mean blood pressure at which autoregulation is effective is approximately 60 mm Hg. Below this level, changes in the caliber of cerebral arteries cannot compensate for decreased perfusion pressure; cerebral blood flow therefore declines, producing symptoms of hypoxia, such as lightheadedness, confusion, and dimming of vision. These symptoms are followed by somnolence and loss of consciousness if the mean blood pressure falls below 35-40 mm Hg. In contrast, at blood pressures above the upper limit of the range of autoregulation (150-200 mm Hg), cerebral blood flow is increased, which can produce hypertensive encephalopathy.

In chronically hypertensive individuals, the lower limit of the autoregulatory range is higher, which may be due to damage to small arterial walls. As a result, cerebral blood flow declines when the mean arterial blood pressure falls below about 120 mm Hg. The clinical relevance of this observation is that blood

pressure should be reduced rarely, if ever – and never to hypotensive levels – in patients with stroke.

2. Chronic hypertension. Chronic hypertension appears to promote structural changes in the walls of penetrating arteries, predisposing them to intracerebral hemorrhage. In 1888, Charcot and Bouchard found minute aneurysms on the small intraparenchymal arteries of hypertensive patients and postulated that aneurysmal rupture led to intracerebral hemorrhage. Subsequently, Ross Russell showed micro aneurysms of small resistance arteries in cerebral sites at which hypertensive hemorrhages occur most commonly. Some aneurysms were surrounded by small areas of hemorrhage, and the aneurysmal walls often showed changes of lipohyalinosis or fibrinoid necrosis. These processes are characterized by destruction of the vessel wall with deposition of fibrinoid material, focal aneurysmal expansion of the involved vessel, thrombotic occlusion, and extravasation of red cells. There is now general agreement that massive cerebral hemorrhage often follows the rupture of either a microaneurysmal or lipohyalinotic segment of a small resistance artery and that the underlying lesion is caused by chronic hypertension.

3. Acute hypertension. In addition to structural changes in the cerebral arterial wall produced by chronic hypertension, acute elevation of blood pressure appears to play a role in the pathogenesis of intracerebral hemorrhage. Although most patients with intracerebral hemorrhage are hypertensive following the event, many have no history of hypertension and lack such signs of hypertensive end-organ disease as left ventricular hypertrophy, retinopathy, or nephropathy. It has therefore been suggested that a sudden increase in blood pressure may itself be sufficient to cause intracerebral hemorrhage, as with amphetamine or cocaine abuse. Acute elevation of blood pressure may also be the immediate precipitating cause of intracerebral hemorrhage in chronically hypertensive patients with Charcot-Bouchard aneurysms.

B. Pathology. Most hypertensive hemorrhages originate in certain areas of predilection, corresponding to long, narrow, penetrating arterial branches along which Charcot-Bouchard aneurysms are found at autopsy. These include the caudate and putaminal branches of the middle cerebral arteries (42%); branches of the basilar artery supplying the pons (16%); thalamic branches of the posterior cerebral arteries (15%); branches of the superior cerebellar arteries supplying the dentate nuclei and the deep white matter of the cerebellum (12%); and some white matter branches of the cerebral arteries (10%), especially in the parieto-occipital and temporallobes.

C. Clinical Findings. Hypertensive hemorrhage occurs without warning, most commonly while the patient is awake. Headache is present in 50% of patients and may be severe; vomiting is common. Blood pressure is elevated after the hemorrhage has occurred. Thus, normal or low blood pressure in a patient with stroke makes the diagnosis of hypertensive hemorrhage unlikely, as does onset before 50 years of age.

Following the hemorrhage, edema surrounding the area of hemorrhage produces clinical worsening over a period of minutes to days. The duration of active bleeding, however, is brief. Once the deficit stabilizes, improvement occurs slowly. Since the deficit is caused principally by hemorrhage and edema, which compress rather than destroy brain tissue, considerable return of neurologic function can occur.

Massive hypertensive hemorrhages may rupture through brain tissue into the ventricles, producing bloody CSF; direct rupture through the cortical mantle is unusual. A fatal outcome is most often due to herniation caused by the combined mass effect of the hematoma and the surrounding edema.

Clinical features vary with the site of hemorrhage.

1. Deep cerebral hemorrhage. The two most common sites of hypertensive hemorrhage are the putamen and the thalamus, which are separated by the posterior limb of the internal capsule. This segment of the internal capsule is traversed by descending motor fibers and ascending sensory fibers, including the optic radiations. Pressure on these fibers from an expanding lateral (putaminal) or medial (thalamic) hematoma produces a contralateral sensorimotor deficit. In general, putaminal hemorrhage leads to a more severe motor deficit and thalamic hemorrhage to a more marked sensory disturbance. Homonymous hemianopia may occur as a transient phenomenon after thalamic hemorrhage and is often a persistent finding in putaminal hemorrhage. In large thalamic hemorrhages, the eyes may deviate downward, as in staring at the tip of the nose, because of impingement on the midbrain center for upward gaze. Aphasia may occur if hemorrhage at either site exerts pressure on the cortical language areas. A separate aphasic syndrome has been described with localized hemorrhage into the thalamus; it carries an excellent prognosis for full recovery.

2. Lobar hemorrhage. Hypertensive hemorrhages also occur in subcortical white matter underlying the frontal, parietal, temporal, and occipital lobes. Symptoms and signs vary according to the location; they can include headache, vomiting, hemiparesis, hemisensory deficits, aphasia, and visual field abnormalities. Seizures are more frequent than with hemorrhages in other locations, while coma is less so.

3. Pontine hemorrhage. With bleeding into the pons, coma occurs within seconds to minutes and usually leads to death within 48 hours. Ocular findings typically include pinpoint pupils. Horizontal eye movements are absent or impaired, but vertical eye movements may be preserved. In some patients, there may be ocular bobbing, a bilateral downbeating excursion of the eyes at about 5-second intervals. Patients are commonly quadriparetic and exhibit decerebrate posturing. Hyperthermia is sometimes present. The hemorrhage usually ruptures into the fourth ventricle, and rostral extension of the hemorrhage into the midbrain with resultant midposition fixed pupils is common. In contrast to the classic presentation of pontine hemorrhage described above, small hemorrhages that

spare the reticular activating system – and that are associated with less severe deficits and excellent recovery – also occur.

4. Cerebellar hemorrhage. The distinctive symptoms of cerebellar hemorrhage (headache, dizziness, vomiting, and the inability to stand or walk) begin suddenly, within minutes after onset of bleeding. While patients may initially be alert or only mildly confused, large hemorrhages lead to coma within 12 hours in 75% of patients and within 24 hours in 90%. When coma is present at the onset, the clinical picture is indistinguishable from that of pontine hemorrhage.

Common ocular findings include impairment of gaze to the side of the lesion or forced deviation away from the lesion caused by pressure on the pontine lateral gaze center. Skew deviation may also occur, in which case the eye ipsilateral to the lesion is depressed. The pupils are small and reactive. Ipsilateral facial weakness of lower motor neuron type occurs in about 50% of cases, but strength in the limbs is normal. Limb ataxia is usually slight or absent. Plantar responses are flexor early in the course but become extensor as the brainstem becomes compromised and the patient deteriorates. Impairment of voluntary or reflex upward gaze indicates upward transtentorial herniation of the cerebellar vermis and midbrain, leading to compression of the pretectum. It implies a poor prognosis.

D. Differential Diagnosis. Putaminal, thalamic, and lobar hypertensive hemorrhages may be difficult to distinguish from cerebral infarctions. To some extent, the presence of severe headache, nausea and vomiting, and impairment of consciousness are useful clues that a hemorrhage may have occurred; the CT scan identifies the underlying disorder definitively.

Brainstem stroke or cerebellar infarction can mimic cerebellar hemorrhage. When cerebellar hemorrhage is a possibility, CT scan or MRI is the most useful diagnostic procedure, since hematomas can be quickly and accurately localized. If neither CT nor MRI is available, vertebral angiography should be performed. The angiogram shows a cerebellar mass effect in about 85% of cases, but the procedure is time-consuming. Bloody CSF will confirm the diagnosis of hemorrhage, but a clear tap does not exclude the possibility of an intracerebellar hematoma-and lumbar puncture may hasten the process of herniation. Lumbar puncture is therefore not advocated if a cerebellar hemorrhage is suspected.

Like cerebellar hemorrhage, acute peripheral vestibulopathy also produces nausea, vomiting, and gait ataxia. Severe headache, impaired consciousness, elevated blood pressure, or later age at onset, however, strongly favors cerebellar hemorrhage.

E. Treatment

1. Surgical treatment

a. Cerebellar decompression. The most important therapeutic intervention in hypertensive hemorrhage is surgical decompression for cerebellar hematomas. Unless this step is taken promptly, there may be a fatal outcome or unexpected deterioration. Note that this procedure may also reverse the neurologic

deficit. Since surgical results are much better for responsive than unresponsive patients, surgery should be performed early in the course when the patient is still conscious.

b. Cerebral decompression. Surgery can be useful when a superficial hemorrhage in the cerebral white matter is large enough to cause a mass effect with shift of midline structures and incipient herniation. The prognosis is directly related to the level of consciousness before the operation, and surgery is usually fruitless in an already comatose patient.

c. Contraindications to surgery. Surgery is not indicated for pontine or deep cerebral hypertensive hemorrhages, since in most cases spontaneous decompression occurs with rupture into the ventricles-and the areas in question are accessible only at the expense of normal overlying brain.

2. Medical measures. The use of antihypertensive agents in acute intracerebral hemorrhage is controversial. Attempts to lower systemic blood pressure may compromise cerebral blood flow and lead to infarction, but continued hypertension may exacerbate cerebral edema. On this basis, it seems reasonable to lower blood pressure to diastolic levels of approximately 100 mm Hg following intracerebral hemorrhage, but this must be done with great care because the cerebral vasculature may be unusually sensitive to antihypertensive agents. The use of nitroglycerin paste (1/2-1 in topically) has an advantage in that if the blood pressure declines excessively, the drug can be wiped off the skin and its effect rapidly terminated. If volume overload is considered to contribute to the hypertension, the judicious use of a diuretic such as furosemide (from 10 mg intravenously in patients unused to the drug to 40 mg intravenously in patients accustomed to receiving it) can be helpful.

There is no other effective medical treatment for intracerebral hemorrhage. Rebleeding at the site of a hypertensive intracerebral hemorrhage is uncommon, and anti fibrinolytic agents are not indicated. Corticosteroids are commonly prescribed to reduce vasogenic edema in patients with intracerebral hemorrhage, but the evidence of their benefit is poor. Antiedema agents provide only temporary benefit.

Other Causes of Intracerebral Hemorrhage

A. Trauma. Intracerebral hemorrhage is a frequent consequence of closed-head trauma. Such hemorrhages may occur under the skull at the site of impact or directly opposite the site of impact (contrecoup injury). The most common locations are the frontal and temporal poles. The appearance of traumatic hemorrhages on CT scans may be delayed for as much as 24 hours after injury; MRI permits earlier detection.

B. Vascular Malformations. Bleeding from cerebral angiomas and aneurysms can lead to both intracerebral and subarachnoid hemorrhage. Angiomas may come to medical attention because of seizures, in which case anticonvulsants are the treatment of choice, or because of bleeding. In the latter instance,

surgical removal is indicated to prevent rebleeding – provided the malformation is surgically accessible. Aneurysms usually present with intracranial hemorrhage but occasionally with compressive focal deficits such as third-nerve palsy.

C. Hemorrhage into Cerebral Infarcts. Some cases of cerebral infarction, especially when embolic in origin, are accompanied by hemorrhage into the infarct.

D. Amphetamine or Cocaine Abuse. Intravenous, intranasal, and oral amphetamine or cocaine use can result in intracerebral hemorrhage, which typically occurs within minutes to hours after the drug is administered. Most such hemorrhages are located in subcortical white matter and may be related to either acute elevation of blood pressure, leading to spontaneous hemorrhage or rupture of a vascular anomaly, or drug-induced arteritis.

E. Cerebral Amyloid Angiopathy. Cerebral amyloid (congophilic) angiopathy is a rare cause of intracerebral hemorrhage. Amyloid deposits are present in the walls of small cortical blood vessels and in the meninges. The disorder is most common in elderly patients (a mean age of 70 years) and typically produces lobar hemorrhages at multiple sites. Some cases are familial.

F. Acute Hemorrhagic Leukoencephalitis. This is a demyelinating and hemorrhagic disorder that characteristically follows a respiratory infection and has a fulminant course resulting in death within several days. Multiple small hemorrhages are found in the brain, and red blood cells may be present in CSF.

G. Hemorrhage into Tumors. Bleeding into primary or metastatic brain tumors is an occasional cause of intracerebral hemorrhage. Tumors associated with hemorrhage include glioblastoma multiforme, melanoma, choriocarcinoma, renal cell carcinoma, and bronchogenic carcinoma. Bleeding into a tumor should be considered when a patient with known cancer experiences acute neurologic deterioration; it may also be the presenting manifestation of cancer.

H. Coagulopathies. Intracerebral hemorrhage is a complication of disorders of both clotting factors and platelets, such as hemophilia (factor VIII deficiency) and idiopathic thrombocytopenic purpura. Acute myelogenous leukemia with white blood cell counts greater than 150,000/μL may also predispose to intracerebral hemorrhage.

I. Anticoagulation. Patients receiving heparin or warfarin are at increased risk for developing spontaneous or traumatic intracerebral hemorrhage.

SUBARACHNOID HEMORRHAGE

Spontaneous (nontraumatic) subarachnoid hemorrhage (bleeding into the subarachnoid space) is usually the result of a ruptured cerebral arterial aneurysm or an AVM. Rupture of a berry aneurysm accounts for about 75% of cases and occurs most often during the fifth and sixth decades, with an approximately

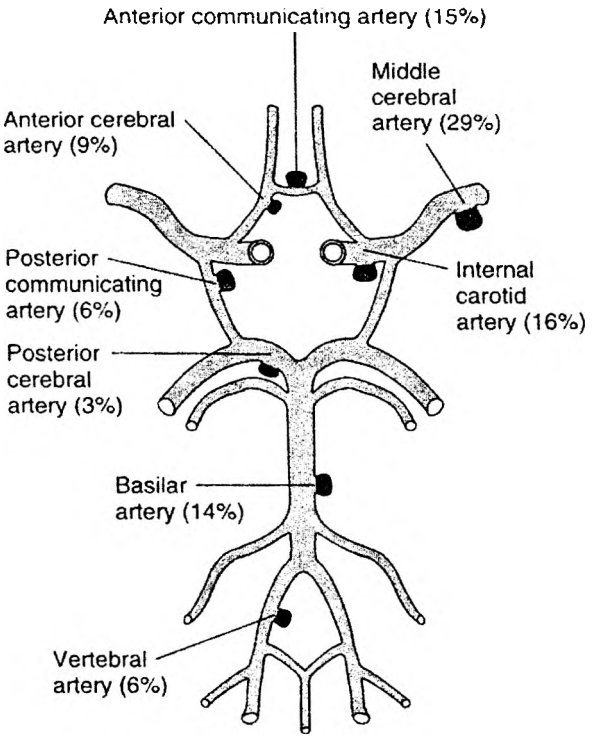


Fig. 17. Frequency and distribution of intracranial aneurysms.

equal sex distribution. Hypertension has not been conclusively demonstrated to predispose to the formation of aneurysms, but acute elevation of blood pressure (eg, at orgasm) may be responsible for their rupture. Intracranial AVMs, a less frequent cause of subarachnoid hemorrhage (10%), occur twice as often in men and usually bleed in the second to fourth decades, although a significant incidence extends into the 60s. Blood in the subarachnoid space can also result from intracerebral hemorrhage, embolic stroke, and trauma.

Pathology

Cerebral artery aneurysms are most commonly congenital "berry" aneurysms, which result from developmental weakness of the vessel wall, especially at sites of branching. These aneurysmal dilatations arise from intracranial arteries about the circle of Willis at the base of the brain and are multiple in about 20% of cases. Other congenital abnormalities, including polycystic kidney disease and coarctation of the aorta, may be associated with berry aneurysms. Occasionally, systemic infections such as infective endocarditis disseminate to a cerebral artery and cause aneurysm formation; such "mycotic" aneurysms account for 2-3% of aneurysmal ruptures. Mycotic aneurysms are usually more distal (along the course of cerebral arteries) than are berry aneurysms.

AVMs consist of abnormal vascular communications that permit arterial blood to enter the venous system without passing through a capillary bed. They are most common in the middle cerebral artery distribution.

Pathophysiology

Rupture of an intracranial artery elevates intracranial pressure and distorts pain-sensitive structures, producing headache. Intracranial pressure may reach systemic perfusion pressure and acutely decrease cerebral blood flow; together with the concussive effect of the rupture, this is thought to cause the loss of consciousness that occurs at the onset in about 50% of patients. Rapid elevation of intracranial pressure can also produce subhyaloid retinal hemorrhages.

Because aneurysmal hemorrhage is usually confined to the subarachnoid space, it does not produce a focal cerebral lesion. Prominent focal findings on neurologic examination are accordingly uncommon except with middle cerebral artery aneurysms. Ruptured AVMs, however, produce focal abnormalities that correspond to their parenchymal location.

Clinical Findings

A. Symptoms and Signs. The classic (but not invariable) presentation of subarachnoid hemorrhage is the sudden onset of an unusually severe generalized headache ("the worst headache I ever had in my life"). The absence of headache essentially precludes the diagnosis. Loss of consciousness is frequent, as are

vomiting and neck stiffness. Symptoms may begin at any time of day and during either rest or exertion.

The most significant feature of the headache is that it is new. Milder but otherwise similar headaches may have occurred in the weeks prior to the acute event. These earlier headaches are probably the result of small prodromal hemorrhages (sentinel, or warning, hemorrhages) or aneurysmal stretch.

The headache is not always severe, however, especially if the subarachnoid hemorrhage is from a ruptured AVM rather than an aneurysm. Although the duration of the hemorrhage is brief, the intensity of the headache may remain unchanged for several days and subside only slowly over the next 2 weeks. A recrudescent headache usually signifies recurrent bleeding.

Blood pressure frequently rises precipitously as a result of the hemorrhage. Meningeal irritation may induce temperature elevations to as high as 39°C during the first 2 weeks. There is frequently confusion, stupor, or coma. Nuchal rigidity and other evidence of meningeal irritation are common, but these signs may not occur for several hours after the onset of the headache. Preretinal globular subhyaloid hemorrhages (found in 20% of cases) are most suggestive of the diagnosis. Because bleeding occurs mainly in the subarachnoid space in patients with aneurysmal rupture, prominent focal signs are uncommon on neurologic examination. When present, they may bear no relationship to the site of the aneurysm. An exception is oculomotor nerve palsy occurring ipsilateral to a posterior communicating artery aneurysm. Bilateral extensor plantar responses and VI nerve palsies are frequent in such cases. Ruptured AVMs may produce focal signs, such as hemiparesis, aphasia, or a defect of the visual fields, that help to localize the intracraniallesion.

B. Laboratory Findings. Patients presenting with subarachnoid hemorrhage are generally investigated first by CT scan, which will usually confirm that hemorrhage has occurred and may help to identify a focal source. CT brain scanning will detect subarachnoid blood in more than 90% of patients with aneurysmal rupture. The test is highly sensitive on the day bleeding occurs; it is most sensitive in patients with altered consciousness. Intracerebral or intraventricular blood, associated hydrocephalus, and infarction can also be identified. Aneurysms may not be evident on the CT scan, but most AVMs can be seen with contrast. MRI is especially useful in detecting small AVMs localized to the brain stem (an area poorly seen on CT scan). If the CT scan fails to confirm the clinical diagnosis of subarachnoid hemorrhage, lumbar puncture is performed.

The CSF examination usually reveals markedly elevated pressure, often above the maximum recordable value (600 mm H_2O) using the standard CSF manometer; the fluid is grossly bloody and contains from 100,000 to more than 1 million red cells/μL. As a result of the breakdown of hemoglobin from red cells, the supematant of the centrifuged CSF becomes yellow (xanthochromic) within several hours (certainly by 12 hours) following the hemorrhage. White cells are initially present in the spinal fluid in the same proportion to red cells as

in the peripheral blood. The chemical meningitis caused by blood in the subarachnoid space, however, may produce a pleocytosis of several thousand white blood cells during the first 48 hours and a reduction in CSF glucose between the fourth and eighth days after the hemorrhage. In the absence of pleocytosis, CSF glucose following subarachnoid hemorrhage is normal. The peripheral blood white count is often modestly elevated but rarely exceeds 15,000 cells/μL. The ECG may reveal a host of abnormalities: peaked or deeply inverted T waves, short PR interval, or tall U waves.

Once the diagnosis is confirmed, four-vessel cerebral arteriography is undertaken. Cerebral angiography of both the carotid and vertebral arteries should be performed to visualize the entire cerebral vascular anatomy, since multiple aneurysms occur in 20% of patients and AVMs are frequently supplied from multiple sources. Angiography can be performed at the earliest time convenient for radiology department personnel; emergency studies in the middle of the night are rarely indicated. Angiography is a prerequisite to the rational planning of surgical treatment and is therefore not necessary for patients who are not surgical candidates, eg, those who are deeply comatose.

Differential Diagnosis

The history of a sudden severe headache with confusion or obtundation, nuchal rigidity, a nonfocal neurologic examination, and bloody spinal fluid is highly specific for subarachnoid hemorrhage.

Hypertensive intracerebral hemorrhage is also manifested by obtundation and hemorrhagic spinal fluid, but there are prominent focal findings. Bacterial meningitis is excluded by the CSF examination. Ruptured mycotic aneurysm is suggested by other signs of endocarditis. Traumatic spinal puncture can be excluded as the cause of bloody CSF by examination of the centrifuged CSF specimen. Since blood that results from traumatic lumbar puncture has not yet undergone enzymatic breakdown to bilirubin, centrifugation of the spinal fluid specimen reveals a colorless supernatant.

Complications & Sequelae

A. Recurrence of Hemorrhage. Recurrence of aneurysmal hemorrhage (20% over 10-14 days) is the major acute complication and roughly doubles the mortality rate. Recurrence of hemorrhage from AVM is less common in the acute period.

B. Intraparenchymal Extension of Hemorrhage. While it is common for hemorrhages from an AVM to involve the cerebral parenchyma, this is far less common with aneurysm. Nevertheless, rupture of an aneurysm of the anterior cerebral or middle cerebral artery may direct a jet of blood into brain parenchyma, producing hemiparesis, aphasia, and sometimes transtentorial herniation.

C. Arterial Vasospasm. Delayed arterial narrowing, termed vasospasm, occurs in vessels surrounded by subarachnoid blood and can lead to parenchy-

mal ischemia in more than one-third of cases. Clinical ischemia typically does not appear before day 4 after the hemorrhage, peaks at day 10-14, and then spontaneously resolves. The diagnosis can be confirmed by transcranial Doppler or cerebral angiography. The severity of spasm is related to the amount of subarachnoid blood, and therefore is less common where less blood is usually seen, such as in traumatic subarachnoid hemorrhage or AVM.

D. Acute or Subacute Hydrocephalus. Acute or subacute hydrocephalus may develop during the first day-or after several weeks-as a result of impaired CSF absorption in the subarachnoid space. Progressive somnolence, nonfocal findings, and impaired upgaze should suggest the diagnosis.

E. Seizures. Seizures occur in fewer than 10% of cases and only following damage to the cerebral hemisphere. Decorticate or decerebrate posturing is common, however, and may be mistaken for seizures.

F. Other Complications. Although inappropriate secretion of antidiuretic hormone and resultant diabetes insipidus can occur, they are uncommon.

Treatment

A. Medical Treatment. Medical treatment is traditionally directed toward preventing elevation of arterial or intracranial pressure that might rerupture the aneurysm or AVM. Typical measures include absolute bed rest with the head of the bed elevated 15-20 degrees, mild sedation, and analgesics for headache. Drugs impairing platelet function (eg, aspirin) should be avoided. Since patients who are hypertensive on admission have an increased mortality risk, reducing the blood pressure (to approximately 160/100 mm Hg) is prudent. Bed rest and mild sedation are often adequate in this regard. Hypotension should be prevented, however, to ensure adequate cerebral perfusion. Intravenous fluids should be administered with care, since overhydration can exacerbate cerebral swelling. Intravenous fluids should be iso-osmotic to minimize free water exacerbating brain edema. Normal saline can be given in amounts to ensure normovolemia. Hyponatremia is frequently seen, and usually represents, at least in part, cerebral salt-wasting; it should be managed with sodium replacement such as NaCl orally or 3% normal saline intravenously rather than fluid restriction. Prophylactic use of the calcium channel antagonist drug **nimodipine,** 60 mg orally (or by nasogastric tube) every 4 hours for 21 days, may reduce the ischemic sequelae of cerebral vasospasm in patients with a ruptured aneurysm. Vasospasm is treated by induced hypertension with phenylephrine or dopamine; this intervention is more safely performed after definitive surgical treatment of the aneurysm. Although seizures are uncommon after aneurysmal rupture, the hypertension accompanying a seizure increases the risk of rerupture; a prophylactic anticonvulsant (eg, phenytoin, 300 mg/d) is therefore recommended routinely.

B. Surgical Treatment:

1. Aneurysm. Definitive surgical therapy consists of clipping the neck of the aneurysm or the endovascular placement of a coil to induce clotting. The neurologic examination is used to grade the patient's clinical state relative to surgical candidacy. In patients who are fully alert (grades I and II) or only mildly confused (grade III), surgery has been shown to improve the clinical outcome. In contrast, stuporous (grade IV) or comatose (grade V) patients do not appear to benefit from the procedures. Although there is some controversy about the optimal timing of surgery, current evidence supports early intervention, within about 2 days following the hemorrhage. This approach reduces the period at risk for rebleeding and permits aggressive treatment of vasospasm with volume expansion and pharmacologic elevation of blood pressure.

2. AVMs. Surgically accessible AVMs may be removed by en bloc resection or obliterated by ligation of feeding vessels or embolization via local intra-arterial catheter. Because the risk of an early second hemorrhage is much less with AVMs than with aneurysms, surgical treatment can be undertaken electively at a convenient time after the bleeding episode.

Prognosis

The mortality rate from aneurysmal subarachnoid hemorrhage is high. About 20% of patients die before reaching a hospital, 25% die subsequently from the initial hemorrhage or its complications, and 20% die from rebleeding if the aneurysm is not surgically corrected. Most deaths occur in the first few days after the hemorrhage. The probability of survival following aneurysmal rupture is related to the patient's state of consciousness and the elapsed time since the hemorrhage. On day I, the prognosis for survival for symptom-free and somnolent patients is, respectively, 60% and 30%; such patients still alive at 1 month have survival probabilities of 90% and 60%, respectively. Recovery from subarachnoid hemorrhage resulting from rupture of intracerebral AVMs occurs in nearly 90% of patients, and although recurrent hemorrhage remains a danger, conservative management compares favorably with surgical therapy.

VASCULAR DEMENTIA

Impairment of blood supply to the brain used to be considered to be the main cause of dementia in the elderly, until it was recognized that such a mechanism is rarely, if ever, implicated. Multiple small strokes, referred to as multi-infarct dementia, were subsequently identified as the principal mechanism,

both clinically and at autopsy. In most neuropathological and clinical series, vascular dementia is the most common cause after Alzheimer's disease, accounting for some 10-20 per cent of dementia cases alone, and an important concomitant of Alzheimer's disease or other degenerative dementias. The incidence of vascular dementia may be falling with better management of vascular risk factors. It is also believed that many cases of dementia with Lewy bodies were previously diagnosed clinically as vascular dementia. If cases of dementia where there is a vascular component are considered, then there is no doubt that vascular disease is a major cause or contributor to cognitive. The term 'vascular dementia' is preferable to 'multiinfarct dementia' as it reflects the considerable heterogeneity of the condition and includes cases due to haemorrhage, small lacunar infarcts, large cortical infarcts, and vasculitides. In comparison to Alzheimer's disease, there is a paucity of epidemiological data on vascular dementia. In part, this is due to the fact that patients with major strokes are often excluded, and yet, in one study, up to 25 per cent of patients 3 months after a stroke were considered to have dementia using DSM-IV criteria, and up to 60 per cent had cognitive impairment.

Clinical criteria for the diagnosis of vascular dementia have been dominated by the development of criteria for Alzheimer's disease. Thus, memory remains as a key component and yet may be relatively less important in vascular dementia. Early criteria assumed that stepwise deterioration and motor abnormalities would be characteristic, and from this was developed the Hachinski score. Patients with a score of 4 or less were considered likely to be degenerative by contrast to those with a score of 7 or more, who were thought to have a multi-infarct dementia. This remains a useful guide, and series have been verified pathologically. More recently, the NINCDS-AIREN criteria have been developed, which require the appearance of cognitive impairment within 3 months of a stroke, or sudden onset and fluctuation of cognitive impairment. In view of the potential contribution of focal neuropsychological deficits from a discrete stroke, the cognitive criteria for dementia are that there should be memory impairment plus at least *two* other domains. There should also be relevant vascular changes on imaging which are thought to be directly related. However, very different proportions of cases are diagnosed as vascular dementia, depending upon the use of NINCDS-AIREN, DSM-IV, or ICD10 criteria.

Three main vascular pathologies are believed to be associated with vascular dementia; namely, single discrete cortical infarcts, multiple infarcts (multi-infarct dementia), and subcortical arteriosclerotic encephalopathy (Binswanger's disease). In reality, these may overlap.

Single discrete infarcts, for example, in right middle cerebral and posterior cerebral artery territories and thalamic infarcts, can present with a picture suggestive of dementia. Much more common, however, is the accumulation of deficits from multiple single cortical and/or subcortical infarcts. Men are more commonly affected than women, and there is usually a vascular history, particu-

larly of hypertension. There is a gradual accumulation of cognitive deficits with episodes of confusion or focal neurology. If there are mainly subcortical infarcts, patients tend to have a subcortical pattern of cognitive deficit with cognitive slowing and additional motor features. Some may develop an extrapyramidal syndrome, and in others a pseudobulbar palsy can be prominent with pathological laughing and crying. Neuropathologically, multiple small subcortical infarcts appear to be more important in vascular dementia than single large infarcts.

Subcortical arteriosclerotic encephalopathy (Binswanger's disease)

Binswanger originally described eight cases of periventricular demyelination and dementia. This was considered a rarity until the advent of neuroimaging, and many patients with white matter changes on scanning acquired this diagnosis. Clinically, the features are very similar to those seen in patients with multiple subcortical infarcts, namely frontal and subcortical cognitive features, dysarthria, and pseudobulbar palsy. Gait impairment may occur early and is characterized by a widebased shuffling gait, in contrast to the narrower base seen in Parkinson's disease. Criteria have been suggested for the diagnosis of Binswanger's disease.

Much confusion has arisen from attempts to diagnose Binswanger's disease from neuroimaging. Non-specific periventricular white matter abnormalities are common both in patients with dementia and in the non-demented elderly, and the term leuko-araiosis has been proposed. Leuko-araiosis appears as low attenuation on CT scan, particularly around the frontal and occipital horns, and as increased signal on T2-weighted MRI. Neuropathologically, there is demyelination, gliosis, and hyalinosis, with fibrinoid necrosis of small blood vessels, similar to that seen in hypertension. Minor degrees of white matter disease are also seen in pure Alzheimer's disease.

Treatment is primarily that of management of vascular disease risk factors such as hypertension, smoking, diabetes, carotid stenosis, and heart disease. There have been few control trials of management of risk factors and its affect on cognition, but treatment of isolated systolic hypertension in the elderly may reduce the incidence of dementia.

Other causes of vascular dementia

Significant cognitive impairment, sufficient to justify the criteria of dementia, can occur after subarachnoid haemorrhage, subdural haematomas, and global ischaemia following cardiac arrest with laminar necrosis and hippocampal cell loss. A variety of vasculitides can also be associated with the early development of cognitive impairment and even present as a dementia; these include systemic lupus erythematosus (SLE) and primary cerebral angiitis, which is usually accompanied by headaches. Sneddon's syndrome is the association of livedo reticularis with cerebrovascular disease, and can present with cognitive

impairment. A number, but not all, are associated with anticardiolipin antibodies.

The rare cases of hereditary cerebral amyloidosis, both of the Icelandic and the Dutch and the Flemish type, can be associated with cognitive impairment, although the salient clinical feature is that of recurrent cerebral haemorrhage. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is characterized by recurrent subcortical ischaemic events with the subsequent development of a pseudobulbar palsy and cognitive impairment. Early symptoms include migraine-like headache and psychiatric disturbance. The MRI scan shows a striking leucoencephalopathy in addition to multiple small infarcts. This condition, which is increasingly recognized, is linked to mutations in the Notch 3 gene.

EPILEPSY, SEIZURES & SYNCOPE

EPISODIC LOSS OF CONSCIOUSNESS

Consciousness is lost when the function of both cerebral hemispheres or of the brainstem reticular activating system is compromised. Episodic dysfunction of these anatomic regions produces transient, and often recurrent, loss of consciousness. There are two major causes of episodic loss of consciousness.

Seizures. These are disorders characterized by excessive or oversynchronized discharges of cerebral neurons.

Syncope. This loss of consciousness is due to a reduced supply of blood to the cerebral hemispheres or brainstem. It can result from pancerebral hypoperfusion caused by vasovagal reflexes, orthostatic hypotension, or decreased cardiac output or from selective hypoperfusion of the brainstem resulting from vertebrobasilar ischemia. It is important to distinguish seizures from syncope because they have different causes, diagnostic approaches, and treatment.

The initial step in evaluating a patient who has suffered a lapse of consciousness is to determine whether the setting in which the event occurred-or associated symptoms or signs-suggests that it was a direct result of a disease requiring prompt attention, such as hypoglycemia, meningitis, head trauma, cardiac arrhythmia, or acute pulmonary embolism. The number of spells and their similarity or dissimilarity should be established. If all spells are identical, then a single pathophysiologic process can be assumed, and the following major differential features should be ascertained.

Phenomena at Onset of Spell

A detailed inquiry should always be made about prodromal and initial symptoms. The often brief, stereotyped premonitory symptoms (aura) at the onset of some seizures may localize the central nervous system abnormality responsible for the seizures.

A. An unambiguous description of a sudden onset of unconsciousness without prodromal features is highly suggestive of seizure.

B. Focal sensory or motor phenomena (eg, involuntary jerking of one hand, hemifacial paresthesias, forced head turning) suggest a seizure originating in the contralateral frontoparietal cortex.

C. A sensation of fear, olfactory or gustatory hallucinations, or visceral or deja vu sensations are commonly associated with seizures originating in the temporal lobe.

D. Progressive lightheadedness, dimming of vision, and faintness, which indicate diffuse central nervous system dysfunction, are associated with decreased cerebral blood flow from any cause (simple faints, cardiac arrhythmias, orthostatic hypotension).

Events During the Spell

A. Generalized tonic-clonic (grand mal, or majormotor) seizures are characterized by loss of consciousness, accompanied initially by tonic stiffening and subsequently by clonic (jerking) movements of the extremities.

B. Cerebral hypoperfusion usually produces flaccid unresponsiveness.

C. Cerebral hypoperfusion can also result in stiffening or jerking movements, especially if hypoperfusion is enhanced because the patient is prevented from falling or otherwise assuming a recumbent posture. Such circulatory events are self-limited and do not require anticonvulsant treatment. Loss of consciousness rarely lasts more than 15 seconds and is not followed by postictal confusion unless prolonged brain ischemia has occurred.

Posture When Loss of Consciousness Occurs

Orthostatic hypotension and simple faints occur in the upright or sitting position. Episodes also (or only) occurring in the lying position suggest seizure or cardiac arrhythmia as a likely cause, although syncope induced by strong emotional stimuli may be responsible.

Relationship to Physical Exertion

Syncope associated with exertion is usually due to cardiac outflow obstruction (eg, aortic stenosis, obstructive hypertrophic cardiomyopathy, atrial myxoma) or arrhythmias.

Phenomena Following the Spell

A. A period of confusion, disorientation, or agitation (postictal state) follows a generalized tonicclonic seizure. The period of confusion is usually brief-lasting only for minutes. While such behavior is often strikingly evident to witnesses, it may not be recalled by the patient.

B. Prolonged alteration of consciousness (prolonged postictal state) may follow status epilepticus. It may also occur after a single seizure in patients with diffuse structural cerebral disease (eg, dementia, mental retardation or encephalitis) or metabolic encephalopathy.

C. Recovery from a simple faint is characterized by a prompt return to consciousness with full lucidity.

SEIZURES

A seizure is a transient disturbance of cerebral function caused by an abnormal neuronal discharge. Epilepsy, a group of disorders characterized by recurrent seizures, is a common cause of episodic loss of consciousness; idiopathic epilepsy affects 0.2-0.4% of the general population.

An actively convulsing patient or a reported seizure in a known epileptic usually poses no diagnostic difficulty. Since most seizures occur outside the hospital unobserved by medical personnel, however, the diagnosis must usually be established retrospectively. The two historic features most suggestive of a seizure are the aura associated with seizures of focal onset and the postictal confusional state that follows generalized tonic-clonic seizures (see below). Neither urinary incontinence nor the occurrence of a few tonic or jerking movements is significant in distinguishing seizures from other causes of transient loss of consciousness, since either can occur also with loss of consciousness from cerebral hypoperfusion.

ETIOLOGY

Seizures can result from either primary central nervous system dysfunction or an underlying metabolic derangement or systemic disease. This distinction is critical, since therapy must be directed at the underlying disorder as well as at seizure control. A list of common neurologic and systemic disorders that induce seizures is presented below. The age of the patient may help in establishing the cause of seizures.

Common causes of seizures of new onset

Primary neurologic disorders

- Benign febrile convulsions of childhood
- Idiopathic epilepsy
- Head trauma
- Stroke or vascular malformations
- Mass lesions
- Meningitis or encephalitis
- HIV encephalopathy

Systemic disorders

- Hypoglycemia
- Hyponatremia
- Hyperosmolar states
- Hypocalcemia
- Uremia

Hepatic encephalopathy
Porphyria
Drug overdose
Drug withdrawal
Global cerebral ischemia
Hypertensive encephalopathy
Eclampsia
Hyperthermia

Primary Neurologic Disorders

A. Benign febrile convulsions of childhood are seizures that occur in 2-4% of children 3 months to 5 years old, usually during the first day of a febrile illness, and in the absence of central nervous system infection (meningitis or encephalitis). There may be a family history of benign febrile convulsions or other types of seizures. Benign febrile convulsions usually last for less than 15 minutes and lack focal features. About two-thirds of patients experience a single seizure, and fewer than one-tenth have more than three. Seizures occurring during the first hour of fever in children less than 18 months old or in children with a family history of febrile seizures are associated with a significant risk for recurrence; 90% of recurrences occur within 2 years of the initial episode. The differential diagnosis includes meningitis and encephalitis and brain abscess; if present, these should be treated as described elsewhere in this volume. Since benign febrile convulsions are usually self-limited, treatment is often unnecessary; prolonged convulsions (15 minutes) can be treated with diazepam, 0.3 mg/kg orally, intramuscularly, or intravenously or 0.6 mg/kg rectally. Such treatment may decrease the risk of recurrence. The probability of developing a chronic seizure disorder is 2-6% and is highest in patients with persistent neurologic abnormalities; prolonged, focal, or multiple seizures; or a family history of nonfebrile seizures. Long-term administration of phenobarbital to reduce the risk of subsequent afebrile seizures is not indicated, since the efficacy of such prophylactic therapy is disputed, and cognitive impairment is a common side effect of treatment.

B. Idiopathic epilepsy for which no specific cause can be established accounts for more than 75% of seizure disorders. Idiopathic epilepsy usually begins between the ages of 5 and 25 years, with more than 75% of patients having their first seizure before age 18 years. Less frequently, idiopathic epilepsy begins in later life, although in this age group seizures are also commonly associated with strokes, tumors, trauma, and systemic or metabolic disorders. Not all patients with a single idiopathic seizure go on to develop recurrent seizures: recurrence rates vary from about 30% to as high as 70% in different series, and may be higher in patients with electroencephalographic abnormalities such as a generalized spike-and-wave pattern, postictal Todd's paralysis (see below), per-

sistent neurologic abnormalities, status epilepticus, or a family history of afebrile seizures.

C. Head trauma is a common cause of epilepsy, especially when it occurs perinatally or is associated with a depressed skull fracture or intracerebral or subdural hematoma. Seizures that occur within the first week after nonpenetrating head injuries are not predictive of a chronic seizure disorder, however. Although patients with serious head injuries are often treated prophylactically with anticonvulsant drugs, this practice has been questioned, since a reduction in the incidence of posttraumatic seizures has not been consistently observed beyond one week of treatment.

D. Stroke affecting the cerebral cortex produces seizures in 5-15% of patients and can occur following thrombotic or embolic infarction or intracerebral hemorrhage. As with head trauma, early seizures are not necessarily indicative of chronic epilepsy, and long-term anticonvulsant therapy is not required. Even without rupturing, vascular malformations may be associated with seizures, presumably as a result of their irritative effects on adjacent brain tissue.

E. Mass lesions, such as brain tumors or abscesses, can present with seizures or produce them later in the course. Glioblastomas, astrocytomas, and meningiomas are the most common tumors associated with seizures, reflecting their high prevalence among tumors that affect the cerebral hemispheres.

F. Meningitis or encephalitis caused by bacterial (eg, Haemophilus influenzae), tuberculous, viral (eg, herpes simplex), fungal, or parasitic (eg, cysticercosis) infections can also cause seizures. Seizures in patients with AIDS are most often associated with AIDS dementia complex, but also with toxoplasmosis or cryptococcal meningitis.

Systemic Disorders

Metabolic and other systemic disorders, including drug-overdose and drug-withdrawal syndromes, may be associated with seizures that abate with correction of the underlying abnormality. In these cases, the patient is not considered to have epilepsy.

A. Hypoglycemia can produce seizures, especially with serum glucose levels of 20-30 mg/dL, but neurologic manifestations of hypoglycemia are also related to the rate at which serum glucose levels fall.

B. Hyponatremia may be associated with seizures at serum sodium levels below 120 meq/L or at higher levels following rapid decline.

C. Hyperosmolar states, including both hyperosmolar nonketotic hyperglycemia and hypernatremia, may lead to seizures when serum osmolality rises above about 330 mosm/L.

D. Hypocalcemia with serum calcium levels in the range of 4.3-9.2 mg/dL can produce seizures with or without tetany.

E. Uremia can cause seizures, especially when it develops rapidly, but this tendency correlates poorly with absolute serum urea nitrogen levels.

F. Hepatic encephalopathy is sometimes accompanied by generalized or multifocal seizures.

G. Porphyria is a disorder of heme biosynthesis that produces both neuropathy and seizures. The latter may be difficult to treat because most anticonvulsants can exacerbate the disorder. As a result, seizures caused by porphyria have traditionally been treated with bromides, 1-2 g orally three times daily (therapeutic serum levels 10-20 meq/L). Toxicity (manifested by rash, gastrointestinal symptoms, psychiatric disturbances, or impaired consciousness) is common. In vitro studies suggest the safety of vigabatrine and gabapentin.

H. Drug overdose can exacerbate epilepsy or cause seizures in nonepileptic patients. Generalized tonic-clonic seizures are most common, but focal or multifocal partial seizures can also occur. The drugs most frequently associated with seizures are antidepressants, antipsychotics, cocaine, insulin, isoniazid, lidocaine, and methylxanthines.

I. Drug withdrawal, especially withdrawal from ethanol or sedative drugs, may be accompanied by one or more generalized tonic-clonic seizures that usually resolve spontaneously. Alcohol withdrawal seizures occur within 48 hours after cessation or reduction of ethanol intake in 90% of cases, and are characterized by brief flurries of one to six attacks that resolve within 12 hours. Acute abstinence from sedative drugs can also produce seizures in patients habituated to more than 600-800 mg/d of secobarbital or equivalent doses of other short-acting sedatives. Seizures from sedative drug withdrawal typically occur 2-4 days after abstinence but may be delayed for up to 1 week. Focal seizures are rarely due to alcohol or sedative drug withdrawal alone; they suggest an additional focal cerebral lesion that requires evaluation.

J. Global cerebral ischemia from cardiac arrest, cardiac arrhythmias, or hypotension may produce, at onset, a few tonic or tonic-clonic movements that resemble seizures, but they probably reflect abnormal brainstem activity instead. Global ischemia may also be associated with spontaneous myoclonus or, after consciousness returns, with myoclonus precipitated by movement (action myoclonus). Partial or generalized tonic-clonic seizures also occur; these may be manifested only by minor movements of the face or eyes and must be treated. Nonetheless, isolated seizures following global cerebral ischemia do not necessarily indicate a poor outcome.

K. Hypertensive encephalopathy may be accompanied by generalized tonic-clonic or partial seizures.

L. Eclampsia refers to the occurrence of seizures or coma in a pregnant woman with hypertension, proteinuria, and edema (preeclampsia). As in hypertensive encephalopathy in nonpregnant patients, cerebral edema, ischemia, and hemorrhage may contribute to neurologic complications. Magnesium sulfate has been widely used to treat eclamptic seizures, and may be superior for this purpose to anticonvulsants such as phenytoin.

M. Hyperthermia can result from infection, exposure (heat stroke), hypothalamic lesions, or drugs such as phencyclidine, as well as anticholinergics or neuroleptics (neuroleptic malignant syndrome) and inhalational anesthetics or neuromuscular blocking agents (malignant hyperthermia). Clinical features of severe hyperthermia (42°C) include seizures, confusional states or coma, shock, and renal failure. Treatment is with antipyretics and artificial cooling to reduce body temperature immediately to 39°C and anticonvulsants and more specific therapy (eg, antibiotics for infection, dantrolene for malignant hyperthermia) where indicated. Patients who survive may be left with ataxia as a result of the special vulnerability of cerebellar neurons to hyperthermia.

CLASSIFICATION & CLINICAL FINDINGS

Generalized seizures

- Tonic-clonic (grand mal)
- Absence (petit mal)
- Other types (tonic, clonic, myoclonic)

Partial seizures

- Simple partial
- Complex partial (temporal lobe, psychomotor)

Generalized Seizures

A. Generalized tonic-clonic seizures are attacks in which consciousness is lost, usually without aura or other warning. When a warning does occur, it usually consists of nonspecific symptoms.

1. Tonic phase – The initial manifestations are unconsciousness and tonic contractions of limb muscles for 10-30 seconds, producing extension of the extremities and arching of the body in apparent opisthotonos. Tonic contraction of the muscles of respiration may produce an expiration induced vocalization (cry or moan) and cyanosis, and contraction of masticatory muscles may cause tongue trauma. The patient falls to the ground and may be injured.

2. Clonic phase – The tonic phase is followed by a clonic (alternating muscle contraction and relaxation) phase of symmetric limb jerking that persists for an additional 30-60 seconds-or longer. Ventilatory efforts return immediately after cessation of the tonic phase, and cyanosis clears. The mouth may froth with saliva. With time, the jerking becomes less frequent, until finally all movements cease and the muscles are flaccid. Sphincteric relaxation or detrusor muscle contraction may produce urinary incontinence. The patient then remains unconscious for a variable period that is seldom longer than 30 minutes.

3. Recovery – As the patient regains consciousness, there is postictal confusion and often headache. Full orientation commonly takes 10-30 minutes – or

even longer in patients with status epilepticus (see below) or preexisting structural or metabolic brain disorders. Physical examination during the postictal state is usually otherwise normal in idiopathic epilepsy or seizures of metabolic origin, except that plantar responses may be transiently extensor (Babinski's sign). The pupils always react to light, even when the patient is unconscious. Transient unilateral weakness (hemiparesis) in the postictal period (Todd's paralysis) should be sought, because such a finding suggests a focal brain lesion as the cause and calls for further investigation.

4. Status epilepticus – In this condition, seizures fail to cease spontaneously or recur so frequently that full consciousness is not restored between successive episodes. Status epilepticus is a medical emergency because it can lead to permanent brain damage – from hyperpyrexia, circulatory collapse, or excitotoxic neuronal damage – if untreated.

B. Absence (petit mal) seizures are genetically transmitted seizures that always begin in childhood and usually do not persist after age 20 years. The spells are characterized by brief loss of consciousness (for 5-10 seconds) without loss of postural tone. Subtle motor manifestations, such as eye blinking or a slight head turning, are common. Automatisms are rare. Full orientation immediately follows cessation of the seizure. There may be as many as several hundred spells daily, leading to impaired school performance and social interactions, so that children may be mistakenly thought to be mentally retarded before the diagnosis of petit mal epilepsy is made. The spells are characteristically inducible by hyperventilation. The EEG shows a characteristic 3/s spike-andwave pattern during the seizures. In most patients with normal intelligence and normal background activity on EEG, absence spells occur only during childhood; in other cases, however, the attacks continue into adult life, either alone or in association with other types of seizures.

C. Other types of generalized seizures include tonic seizures (not followed by a clonic phase), clonic seizures (not preceded by a tonic phase), and myoclonic seizures.

1. Tonic seizures are characterized by continuing muscle contraction that can lead to fixation of the limbs and to deviation of the head and eyes to one side; the accompanying arrest of ventilatory movements leads to cyanosis. Consciousness is lost, and there is no clonic phase to these seizures.

2. Clonic seizures are characterized by repetitive clonic jerking accompanied by loss of consciousness. There is no initial tonic component.

3. Myoclonic seizures are characterized by sudden, brief, shocklike contractions that may be localized to a few muscles or one or more extremities or that may have a more generalized distribution. Myoclonic seizures may be idiopathic or associated with a variety of rare hereditary neurodegenerative disorders, including Unverricht-Lundborg disease, Lafora body disease, neuronal ceroid lipofuscinosis (late infantile, juvenile, and adult forms), sialidosis, and

mitochondrial encephalomyopathy (myoclonus epilepsy with ragged red fibers on skeletal muscle biopsy). Not all myoclonic jerks have an epileptic basis.

Partial Seizures

A. Simple partial seizures begin with motor, sensory, or autonomic phenomena, depending on the cortical region affected. For example, clonic movements of a single muscle group in the face, a limb, or the pharynx may occur and may be self-limited; they may be recurrent or continuous or may spread to involve contiguous regions of the motor cortex (jacksonian march).

Autonomic symptoms may consist of pallor, flushing, sweating, piloerection, pupillary dilatation, vomiting, borborygmi, and incontinence. Psychic symptoms include dysphasia, distortions of memory (eg, deja vu, the sensation that a new experience is being repeated), forced thinking or labored thought processes, cognitive deficits, affective disturbances (eg, fear, depression, an inappropriate sense of pleasure), hallucinations, or illusions. During simple partial seizures, consciousness is preserved unless the seizure discharge spreads to other areas of the brain, producing tonic-clonic seizures (secondary generalization). The aura is the portion of the seizure that precedes loss of consciousness and of which the patient retains some memory. The aura is sometimes the sole manifestation of the epileptic discharge.

In the postictal state, a focal neurologic deficit such as hemiparesis (Todd's paralysis) that resolves over a period of ½-36 hours is a manifestation of an underlying focal brain lesion.

B. Complex partial seizures, formerly called temporal lobe or psychomotor seizures, consist of episodes in which consciousness is impaired but not lost. The seizure discharge usually arises from the temporal lobe or medial frontal lobe. The symptoms take many forms but are usually stereotyped for the individual patient. Epigastric sensations are most common, but affective (fear), cognitive (deja vu), and sensory (olfactory hallucinations) symptoms also occur. Consciousness is then impaired. Seizures generally persist for less than 30 minutes (on the average, 1-3 minutes). The motor manifestations of complex partial seizures are characterized by coordinated involuntary motor activity, termed automatism, which takes the form of orobuccolingual movements in about 75% of patients and other facial or neck movements in about 50%. Sitting up or standing, fumbling with objects, and bilateral limb movements are less common. Secondary generalization may occur.

DIAGNOSIS

The diagnosis of seizures is based on clinical recognition of one of the seizure types described above. The EEG can be a helpful confirmatory test in distinguishing seizures from other causes of loss of consciousness. On the other

hand, however, a normal or nonspecifically abnormal EEG never excludes the diagnosis of seizures. Specific EEG features that suggest epilepsy include abnormal spikes, polyspike discharges, and spike-wave complexes.

A standard diagnostic evaluation of patients with recent onset of seizures is presented below. Metabolic and toxic disorders should be excluded, because they do not require anticonvulsants.

Seizures with a clearly focal onset or those that begin after age 25 years require prompt evaluation to exclude the presence of a structural brain lesion. MRI is essential for this purpose (CT is not adequate). If no cause is found, the decision to begin chronic anticonvulsant therapy should be based on the probability of recurrence. Following a single generalized tonic-clonic seizure, recurrence can be expected within 3-4 years in 30-70% of untreated adult patients.

Evaluation of a new seizure disorder in a stable patient

History (including medications or drug exposure)
General physical examination
Complete neurologic examination
Blood studies
- Fasting glucose
- Serum calcium
- Serum FT A-ABS
- Serum electrolytes
- Complete blood count
- Erythrocyte sedimentation rate
- Renal function studies
- Hepatic function studies

EEG
CT brain scan or MRI (especially with abnormal examination, progressive disorder, or onset of seizures after 25 years of age)

SELECTION OF THERAPY

Therapy should be directed toward the cause of the seizures, if known. Seizures associated with metabolic and systemic disorders usually respond poorly to anticonvulsants but cease with correction of the underlying abnormality. Acute withdrawal from alcohol and other sedative drugs produces self-limited seizures that, in general, require no anticonvulsant drug therapy. Acute head trauma and other structural brain lesions that result in seizures must be rapidly diagnosed and treated, and the associated seizures controlled by anticonvulsant drug therapy. Idiopathic epilepsy is treated with anticonvulsant medications.

Anticonvulsant Drug Treatment

Commonly used anticonvulsant drugs and their dosages and methods of administration are listed below. There are four key principles of management:

Establish the diagnosis of epilepsy before starting drug therapy. Therapeutic trials of anticonvulsant drugs intended to establish or reject a diagnosis of epilepsy may yield incorrect diagnoses.

Choose the right drug for the seizure type. Absence seizures, for example, do not respond to most drugs used for complex partial or generalized tonic-clonic seizures.

Treat the seizures, rather than the serum drug levels. Control of seizures is achieved at different drug levels in different patients.

Evaluate one drug at a time. In most cases, seizures can be controlled with a single drug. Therefore, beginning therapy with multiple drugs may expose patients to increased drug toxicity without added therapeutic benefit.

Most patients with epilepsy fall into one of the following treatment categories.

A. New Seizures. Most epileptologists do not recommend chronic anticonvulsant drug treatment following a single seizure unless an underlying cause is found that is not correctable and is likely to produce recurrent seizures (eg, brain tumor). However, recurrent seizures do require anticonvulsant treatment, and if such therapy is to be administered, the oral loading schedules can be used. Note that starting a drug at its daily maintenance dose produces stable serum drug levels only after approximately five half-lives have elapsed. Therefore, loading doses should be given whenever possible to achieve therapeutic drug levels promptly in patients with frequent seizures. Phenytoin, carbamazepine, or valproic acid is the current drug of first choice for treating generalized tonic-clonic or partial seizures in adults, and valproic acid or carbamazepine is preferred for children. Phenobarbital is also very effective in treating generalized tonicclonic seizures in adults, but it is less helpful for treatment of complex partial seizures.

The newer anticonvulsants gabapentin, lamotrigine, topiramate, vigabatrin, and tiagabine may be helpful for patients who respond suboptimally to conventional anticonvulsant drugs.

Absence attacks of the petit mal variety are treated with valproic acid or ethosuximide. The former has the advantage of also providing protection against tonic-clonic seizures but has caused fatalities from hepatic damage in children under 10 (usually under 2) years of age.

Myoclonic seizures are treated with valproic acid or clonazepam.

B. Recurrent Seizures on Drug Therapy:

1. Determining serum levels of drugs. Blood levels of the anticonvulsant drugs the patient has been taking should be measured in samples taken just prior to a scheduled dose. For a single seizure no acute change in medication is man-

dated even if there has been no interruption of drug therapy and anticonvulsant drug levels are in the therapeutic range, but a slight increase in prescribed dose may be considered. If the history or serum drug levels suggest that treatment has been interrupted, the prescribed drug should be started again as for new seizures.

2. Changing to a second drug. A second anticonvulsant should be introduced only if seizures continue to occur after maximum therapeutic benefit has been achieved with the initial drug. This means not only that blood levels of the drug are in the therapeutic range but also that drug toxicity precludes further dosage increments. An anticonvulsant that has failed to alter seizure frequency should be discontinued gradually once therapeutic levels of the second drug have been achieved. If the first drug has produced partial control of the seizure disorder, however, it is often continued along with the second drug.

3. Treating refractory seizures. In some patients, disabling seizures persist despite trials of all major anticonvulsants, alone and in combination – and at the highest doses the patient can tolerate. When no treatable cause can be found, seizures are not due to a progressive neurodegenerative disease, and medical treatment has been unsuccessful for at least 2 years, evaluation for possible surgical therapy should be considered. Presurgical evaluation begins with a detailed history and neurologic examination to explore the cause of seizures and their site of origin within the brain and to document the adequacy of prior attempts at medical treatment. MRI and electrophysiologic studies are performed to identify the epileptogenic zone within the brain. Several electrophysiologic techniques can be used: EEG, in which cerebral electrical activity is recorded from the scalp; stereotactic depth electrode EEG, in which activity is recorded from electrodes inserted into the brain; and electrocorticography, which involves intraoperative recording from the surface of the brain. When an epileptogenic zone can be identified in this manner and its removal is not expected to produce undue neurologic impairment, surgical excision may be indicated. Patients with complex partial seizures arising from a single temporal lobe are the most frequent surgical candidates; unilateral anterior temporal lobectomy abolishes seizures in about 50% of these patients and significantly reduces their frequency in another 25%. Hemispherectomy and corpus callosum section are also sometimes used to treat intractable epilepsy.

C. Multiple Seizures or Status Epilepticus.

1. Early management

a. Immediate attention should be given to ensuring that the airway is patent and the patient positioned to prevent aspiration of stomach contents.

b. The laboratory studies listed earlier should be ordered without delay.

c. Dextrose, 50 mL of 50% solution, should be given intravenously.

d. If fever or meningeal signs are present, immediate lumbar puncture is mandatory, and a gramstained smear of spinal fluid should be examined to exclude bacterial meningitis. Patients without these signs should also undergo lumbar puncture if the cause of the seizures has not been determined (eg, by

their cessation upon administration of dextrose), unless signs of increased intracranial pressure or of focal brain dysfunction are present. It should be noted that postictal pleocytosis is detectable in CSF in approximately 2% of patients with single generalized tonic-clonic seizures (and about 15% of those with status epileptic us) in the absence of infection. The white blood cell count may be as high as 80/μL, with either polymorphonuclear or mononuclear predominance. Serum protein content may be slightly elevated, but glucose concentration is normal, and Gram's stain is negative. The postictal pleocytosis resolves in 2-5 days.

2. Drug therapy to control seizures. Every effort must be made to establish a precise etiologic diagnosis so that treatment of the underlying disorder can be started. Because generalized seizure activity per se damages the brain if it persists for more than 1-2 hours, drug therapy to terminate seizures should be instituted immediately.

Anticonvulsants

Drugs	Preparation, mg	Dosage	
		Loading Mg/d	Maintenance Mg/d
Phenytoin	100	1000	300-400
Carbamazepine	200, 400	400	600-1600
Phenobarbital	100		90-180
Valproic acid	250	750-3000	750-3000
Ethosuximide	250	15 mg/kg/d	15-40 mg/kg/d
Clonazepam	0.5	1.5	1.5-20
Gabapentin	100, 400	300	900-4800
Lamotrigine	50, 100, 200	25	200-500
Vigabatrin	500	1000	2-4 g
Topiramate	25, 100, 200	25	200-400
Oxcarbazepine	150, 300, 600	600	1200
Levetiracetam	250, 500	1000	1000-3000

Emergency evaluation of serial seizures, or status epilepticus

- Treatment with anticonvulsants should be instituted immediately, while the following measures are taken
- Vital signs:
  - Blood pressure: exclude hypertensive encephalopathy and shock
  - Temperature: exclude hyperthermia
  - Pulse: exclude life-threatening cardiac arrhythmia

- Draw venous blood for serum glucose, calcium, electrolytes, hepatic and renal function blood studies, complete blood count, erythrocyte sedimentation rate, and toxicology
- Insert intravenous line
- Administer glucose (50 mL of 50% dextrose) intravenously
- Obtain any available history
- Rapid physical examination, especially for
    - Signs of trauma
    - Signs of meningeal irritation or systemic infection
    - Papilledema
    - Focal neurologic signs
    - Evidence of metastatic, hepatic, or renal disease
- Arterial blood gases
- Lumbar puncture, unless the cause of seizures has already been determined or signs of increased intracranial pressure or focal neurologic signs are present
- ECG
- Calculate serum osmolality: 2 (serum sodium concentration) + serum glucose/20 + serum urea nitrogen/3 (normal range: 270-290)
- Urine sample for toxicology, if indicated

3. Management of hyperthermia. The metabolic consequences of status epilepticus are related to increased motor activity and high levels of circulating catecholamines; they include hyperthermia (to 42-43 °C), lactic acidosis (to pH <7.00), and peripheral blood leukocytosis (to 60,000 cells/μL). These derangements typically resolve over a few hours after cessation of the seizures. Only hyperthermia, which is known to increase the risk of brain damage from status epilepticus, requires specific attention.

Severe hyperthermia must be treated with a cooling blanket and, if necessary, the induction of motor paralysis with a neuromuscular blocking agent such as curare. Mild or moderate hyperthermia, not requiring specific intervention, may persist for 24-48 hours. Lactic acidosis resolves spontaneously over 1 hour and should not be treated. Infection should, of course, be excluded.

Discontinuance of Anticonvulsants

Patients (usually children) with epilepsy who are seizure-free on medication for 2-5 years may wish to discontinue anticonvulsant drugs. In patients with normal intelligence and a normal neurologic examination, the risk of seizure recurrence may be as low as 25%. Risk factors for recurrence include slowing or spikes (maximum risk with both present) on EEG. When anticonvulsants are to be withdrawn, one drug is eliminated at a time by tapering the dose slowly over 6 weeks. Recurrence of seizures has been reported in approximately 20% of

children and 40% of adults following medication withdrawal, in which case prior medication should be reinstituted at the previously effective levels.

COMPLICATIONS OF EPILEPSY & ANTICONVULSANT THERAPY

Complications of Epilepsy

When the diagnosis of epilepsy is made, the patient should be warned against working around moving machinery or at heights and reminded of the risks of swimming alone. The issue of driving must also be addressed. Many state governments have notification requirements when a diagnosis of epilepsy is made.

Side Effects of Anticonvulsant Drugs

All anticonvulsant drugs may lead to blood dyscrasias, but carbamazepine and valproic acid have been associated with the highest incidence of hematologic – and hepatic – toxicity. For this reason, a complete blood count and liver function tests should be obtained before initiating administration of these drugs and at intervals during the course of treatment. The authors recommend performing these tests at 2 weeks, 1 month, 3 months, 6 months, and every 6 months thereafter. Carbamazepine should be discontinued if the total neutrophil count falls below 1,500/ml or if aplastic anemia is suspected. Valproic acid should be terminated if symptoms of hepatotoxicity, such as nausea, vomiting, anorexia or jaundice occur. Lamotrigine has a 1:1,000 incidence of Stevens-Johnson syndrome in the first 8 weeks. Most anticonvulsant drugs (especially barbiturates) affect cognitive function to some degree, even in therapeutic doses.

A variety of drugs alter the absorption or metabolism of anticonvulsants when given concomitantly.

Epilepsy & Anticonvulsant in Pregnancy

The incidence of stillbirth, microcephaly, mental retardation, and seizure disorders is increased in children born to epileptic mothers. Anticonvulsant therapy during pregnancy, however, is also associated with a greater than normal frequency of congenital malformations – specially cleft palate, cleft lip, and cardiac anomalies. Such malfonnations are about twice as common in the offspring of medicated as of unmedicated epileptic mothers, but since patients with more severe epilepsy are more likely to be treated, it is difficult to know whether epilepsy or its treatment is the more important risk factor.

Among commonly used anticonvulsants, valproic acid and to some degree carbamazepine are associated with an increased incidence of neural tube defects (2% and 0.5%, respectively). Phenobarbital and phenytoin pose some teratogenic risk, but the extent of the risk is controversial. The fetal risks of the newer anticonvulsants are not known.

When an epileptic patient who has been seizurefree for several years is contemplating pregnancy, an attempt should be made to withdraw anticonvulsants prior to conception. If anticonvulsant drugs are absolutely required, carbamazepine is thought to have the lowest fetal risk and continues to be recommended for generalized tonic-clonic seizures, and ethosuximide for absence seizures. In contrast to generalized tonic-clonic seizures, partial and absence seizures present little risk to the fetus, and it may be possible to tolerate imperfect control of these seizures during pregnancy to avoid fetal drug exposure. Clonazepam can also be used; but phenytoin, phenobarbital, and primidone should be avoided if possible, and trimethadione and valproic acid should not be used. Every effort should be made to control the seizures with a single drug. Status epilepticus is treated as described above for nonpregnant patients.

Plasma levels of anticonvulsant drugs may decrease during pregnancy because of the patient's enhanced metabolism, and higher doses may be required to maintain control of seizures. It is therefore important to monitor drug levels closely in this setting.

PROGNOSIS

After a single unprovoked seizure, only one-third to one-half of patients will have a recurrence (develop epilepsy). If a second seizure occurs, however, the recurrence rate approaches 75% and anticonvulsants should therefore be started. With appropriate anticonvulsant drug treatment, seizures can be well controlled, although not always eliminated, in most epileptic patients. At the onset of treatment patients should be seen every few months to monitor seizure frequency and make dose adjustments.

PSEUDOSEIZURES

Attacks that resemble seizures (psychogenic seizures, or pseudoseizures) may be manifestations of a psychiatric disturbance such as conversion disorder, somatization disorder, factitious disorder with physical symptoms, or malingering. In conversion or somatization disorder, the patient is unaware of the psychogenic nature of symptoms and the motivation for their production. In factitious disorder, the patient recognizes that the spells are self-induced, but not the reason for doing so. In malingering, there is conscious awareness of both the production of symptoms and the underlying motivation.

Pseudoseizures can usually be distinguished both clinically and by the EEG findings. In patients with pseudoseizures resembling tonic-clonic attacks, there may be warning and preparation before the attack; there is usually no tonic phase, and the clonic phase consists of wild thrashing movements during which the patient rarely comes to harm or is incontinent. In some instances, there are abnormal movements of all extremities without loss of consciousness; in others,

there is shouting or obscene utterances during apparent loss of consciousness or goal-directed behavior. There is no postictal confusion or abnormal clinical signs following the attack. The EEG recorded during the episode does not show organized seizure activity, and postictal slowing does not occur. The differential diagnosis should include, however, frontal lobe seizures, which may be marked by unusual midline movements (pelvic thrusting, bicycling) and by very brief postictal states. Ictal EEG abnormalities may escape detection as well.

It is important to appreciate that many patients with pseudoseizures also have genuine epileptic attacks that require anticonvulsant medications, but these should be prescribed at an empirically appropriate dose. Psychiatric referral may be helpful.

SYNCOPE

VASOVAGAL SYNCOPE (SIMPLE FAINTS)

Vasovagal disorders, which are exceedingly common, occur in all age groups and affect men and women equally. Precipitating factors include emotional stimulation, pain, the sight of blood, fatigue, medical instrumentation, blood loss, or prolonged motionless standing. Vagally mediated decreases in arterial blood pressure and heart rate combine to produce central nervous system hypoperfusion and subsequent syncope. Severe cerebral ischemia resulting in tonic-clonic movements can occur if the unconscious patient remains in an upright position during the episode (eg, fainting in a toilet stall).

Vasovagal episodes generally begin while the patient is in a standing or sitting position and only rarely in a horizontal position (eg, with phlebotomy or IUD insertion). A prodrome lasting 10 seconds to a few minutes usually precedes syncope and can include lassitude, lightheadedness, nausea, pallor, diaphoresis, salivation, blurred vision, and tachycardia. The patient, who then loses consciousness and falls to the ground, is pale and diaphoretic and has dilated pupils. Bradycardia replaces tachycardia as consciousness is lost. During unconsciousness, abnormal movements may occur; these are mainly tonic or opisthotonic, but seizurelike tonic-clonic activity is occasionally seen, which can lead to a misdiagnosis of epilepsy. Urinary incontinence may also occur.

The patient recovers consciousness very rapidly (seconds to a few minutes) after assuming the horizontal position, but residual nervousness, dizziness, headache, nausea, pallor, diaphoresis, and an urge to defecate may be noted. A postictal confusional state with disorientation and agitation either is very brief « 30 seconds) or does not occur. Syncope may recur, especially if the patient stands up within the next 30 minutes.

Reassurance and a recommendation to avoid precipitating factors are usually the only treatment necessary.

Recurrent vasovagal syncope (often termed neurocardiogenic syncope) can be documented by head-up tilt-testing. The bradycardia and hypotension can be ameliorated by oral metoprolol, theophylline, or disopyramide; artificial pacing is ineffective against the syncope.

CARDIOVASCULAR SYNCOPE

A cardiovascular cause is suggested when syncope occurs with the patient in a recumbent position, during or following physical exertion, or in a patient with known heart disease. Loss of consciousness related to cardiac disease is most often due to an abrupt decrease in cardiac output with subsequent cerebral hypoperfusion. Such cardiac dysfunction can result from cardiac arrest, rhythm disturbances (either brady- or tachyarrhythmias), cardiac inflow or outflow obstruction, intracardiac right-to-left shunts, leaking or dissecting aortic aneurysms, or acute pulmonary embolus.

1. CARDIAC ARREST

Cardiac arrest (ventricular fibrillation, or asystole) from any cause will cause loss of consciousness in 3-5 seconds if the patient is standing or within 15 seconds if the patient is recumbent. Seizurelike activity and urinary and fecal incontinence may be seen as the duration of cerebral hypoperfusion increases.

2. TACHY ARRHYTHMIAS

Supraventricular Tachyarrhythmias

Supraventricular tachyarrhythmias (atrial or junctional tachycardia, atrial flutter, or atrial fibrillation) may be paroxysmal or chronic and can occur in all age groups – and in persons with or without clinical heart disease. Such rhythm disturbances may be spontaneous, or they may be secondary to metabolic abnormalities, hypoxia, drug overdose, and many systemic and cardiovascular disorders.

Heart rates faster than 160-200/min reduce cardiac output by decreasing the ventricular filling period or inducing myocardial ischemia. Prolonged tachycardia of 180-200 beats or more per minute will produce syncope in 50% of normal persons in the upright posture; in patients with underlying heart disease, a heart rate of 135/min may impair cardiac output enough to induce loss of consciousness. In addition, patients with sinus node dysfunction (sick-sinus syndrome) may develop profound sinus, junctional, or idioventricular bradycardias

– or even asystole – upon termination of their tachyarrhythmias. This can cause syncope, atrial fibrillation, and other forms of atrioventricular dissociation and further reduce cardiac output by loss of coordinated atrial activity.

Routine ECGs, even if abnormal, are often not helpful in establishing a diagnosis, which is firmly established only when arrhythmias are demonstrated during a symptomatic episode. Continuous ECG monitoring or outpatient portable Holter monitoring may be required. Event monitors triggered by the patient at the onset of prodromal symptoms are often particularly helpful.

Ventricular Tachyarrhythmias

Ventricular tachyarrhythmias (ventricular tachycardia or multiform, frequent, or paired premature ventricular contractions) are found on prolonged ECG monitoring in some patients with syncope. The syncope associated with ventricular tachycardia is characterized by a very brief prodrome (less than 5 seconds). Frequent or repetitive premature ventricular contractions alone do not often coincide with syncopal symptoms but are predictive of sudden death.

Mitral Valve Prolapse

Mitral valve prolapse (click-murmur syndrome) is a common disorder associated with supraventricular and ventricular arrhythmias. In one series, 25% of patients reported lightheadedness or dizziness and 4% had syncope. The condition is twice as frequent in women as in men. Atypical chest pain that is characteristically nonexertional, left precordial, sharp in quality, and of variable duration is the most common complaint, followed by dyspnea and fatigue. Serious ventricular arrhythmias and profound bradycardia may occur.

Auscultation of the heart may reveal midsystolic clicks, mid-to-late systolic murmurs that vary with specific maneuvers, or a classic mitral regurgitation murmur. The ECG may be entirely normal or may show nonspecific ST-T wave changes. Frequent premature ventricular contractions are often noted. The diagnosis can be established by echocardiography.

Prolonged QT Syndrome

The congenital prolonged QT-interval syndrome consists of paroxysmal ventricular arrhythmias (often torsade de pointes), syncope, and sudden death and is inherited either as an autosomal recessive condition associated with deafness or in an autosomal dominant form without deafness. Sporadic nonfamilial cases have also been reported. Drugs such as quinidine and electrolyte disturbances such as hypocalcemia or hypokalemia can also produce QT prolongation.

Symptoms generally begin in infancy, but patients may be asymptomatic until the second or third decade, especially in the dominantly inherited disorder. Recurrent spells have been confused with epilepsy. The ECG may occasionally show a normal QTc interval at rest that becomes abnormally prolonged with exercise. Treatment with propranolol is often effective.

3. BRADYARRHYTHMIAS

Sinoatrial Node Disease

Sinoatrial node disease may present as profound sinus bradycardia, prolonged sinus pauses, or sinus arrest with the appearance of a slow atrial, junctional, or idioventricular escape rhythm. Patients with sinus node dysfunction may also develop profound bradycardia or asystole sufficient to produce syncope upon termination of a supraventricular tachycardia. Sinus node dysfunction may be idiopathic or the result of fibrosis, vascular occlusion, infiltrative processes, or drug therapy (especially propranolol). All such patients should be promptly evaluated by a cardiologist, since a permanent pacemaker is necessary in many cases.

Complete Heart Block

Complete heart block (third-degree atrioventricular block) is the most common bradyarrhythmia that produces syncope. Permanent atrioventricular conduction abnormalities are easily noted on a routine ECG, but intermittent conduction abnormalities may not be present on a random tracing. Transient complete heart block is suggested as the cause of syncope by an ECG demonstrating bundle branch block with or without a prolonged PR interval or by a syncopal prodrome of less than 5 seconds. A normal PR interval on an ECG obtained after the episode does not exclude the diagnosis of transient complete heart block. Patients with syncope and documented or suspected complete heart block should be promptly hospitalized. Patients with acute inferior myocardial infarctions are at high risk for atrioventricular block.

4. CARDIAC INFLOW OBSTRUCTION

Atrial or ventricular myxomas and atrial thrombi usually present with embolic events, but they may also produce a left ventricular inflow or outflow obstruction that results in a sudden decrease in cardiac output, followed by syncope. Physical examination of the patient with left atrial myxoma often suggests mitral stenosis, but a mitral regurgitation murmur is occasionally heard. Fever, petechiae, and an elevated sedimentation rate may also be present. A history of syncope occurring with change in position is classic but uncommon. Echocardiography can confirm the diagnosis. Surgical removal of the myxoma is indicated. With constrictive pericarditis or pericardial tamponade, any maneuver or drug that decreases heart rate or venous return can result in suddenly inadequate cardiac output and syncope.

5. CARDIAC OUTFLOW OBSTRUCTION

Aortic Stenosis

Loss of consciousness from congenital or acquired severe aortic stenosis occurs in all age groups, usually following exercise, and is often associated with dyspnea, angina, and diaphoresis. Several pathophysiologic processes have been hypothesized, including acute left ventricular failure resulting in coronary hypoperfusion, with subsequent ventricular fibrillation. Alternatively, abrupt increases in left ventricular pressure may stimulate baroreceptors, leading to reflexive peripheral vascular dilation. Physical findings include a characteristic systolic murmur (often associated with a palpable thrill), a sustained and prolonged left ventricular lift, and a paradoxically split second heart sound. Calcification of the valve is usually evident in imaging studies in patients over age 35 years. Echocardiography can help confirm the diagnosis. Symptomatic aortic stenosis associated with angina, congestive heart failure, or syncope requires valve replacement, and all such patients should be promptly hospitalized. The average survival following syncope from aortic stenosis is 18 months to 3 years without treatment.

Pulmonary Stenosis

Severe pulmonary stenosis can produce syncope, especially following exertion. A hemodynamic process similar to that occurring in aortic stenosis is responsible.

Obstructive Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy in its obstructive form (asymmetric septal hypertrophy, hypertrophic cardiomyopathy, idiopathic hypertrophic subaortic stenosis) comprises a group of congenital cardiomyopathies inherited as autosomal dominant conditions of variable severity. Symptoms most often have their onset between the second and fourth decades; dyspnea is the most common presenting complaint (60% of patients), but syncope occurs in 30% and is the presenting complaint in 10%. Syncope characteristically develops during or following exercise, but orthostatic and posttussive episodes also occur. Loss of consciousness has been attributed to left ventricular outflow obstruction caused by abnormal movement of the anterior mitral leaflet against the septum in midsystole, by inflow obstruction from decreased ventricular compliance, or by transient arrhythmias.

Suggestive features on physical examination include a double apical and carotid impulse, a precordial thrill, a prominent fourth heart sound, and a left ventricular heave. The classic long systolic ejection murmur is heard best at the lower left sternal border or apex, radiates poorly into the neck, and has a prominent midsystolic accentuation. Mitral valve prolapse is common, and a mitral

regurgitation murmur may be noted. Unlike valvular aortic stenosis, the murmur increases under circumstances that reduce the volume of the ventricle or increase its contractility (eg, Valsalva's maneuver, amyl nitrite inhalation, or a premature ventricular contraction). If obstructive hypertrophic cardiomyopathy is suspected, the diagnosis can be confirmed by echocardiography. Propranolol has been used successfully to control symptoms.

6. DISSECTING AORTIC ANEURYSM

Approximately 5-10% of patients with acute aortic dissections present with isolated syncope; other neurologic abnormalities mayor may not be present. In 15% of patients, the dissection is painless.

7. PULMONARY HYPERTENSION & PULMONARY EMBOLUS

Syncope, often exertional, may be the presenting symptom of pulmonary hypertension. Signs of right ventricular failure (parasternal heave, increased second heart sound, murmur of pulmonary insufficiency), electrocardiographic evidence of right ventricular hypertrophy, and tachypnea may be found. Unrecognized showers of pulmonary emboli can cause pulmonary hypertension, as can a host of systemic, cardiac, and primary pulmonary diseases. A history of exertional dyspnea is usual, and hypoxemia on blood gas analysis is present even at rest. Syncope is the presenting symptom in about 20% of patients experiencing a massive pulmonary embolus; it is uncommonly a result of small pulmonary emboli. Upon recovery from syncope, such patients often complain of pleuritic chest pain, dyspnea, and apprehension. Hypotension, tachycardia, tachypnea, and significant arterial hypoxia frequently accompany these large emboli.

CEREBROVASCULAR SYNCOPE

Cerebrovascular disease is an often suspected but actually uncommon cause of episodic unconsciousness.

1. BASILAR ARTERY INSUFFICIENCY

Basilar artery transient ischemic attacks usually occur after the sixth decade. The symptom complex of diplopia, vertigo, dysphagia, dysarthria, various sensory or motor symptoms, drop attacks, and occipital headaches suggests diffuse brainstem ischemia. Attacks are typically sudden in onset and brief in du-

ration (seconds to minutes), but when consciousness is lost, recovery is frequently prolonged (30-60 minutes or longer). Isolated unconsciousness without other symptoms of brainstem ischemia is rarely due to basilar artery insufficiency. Two-thirds of patients have recurrent attacks, and strokes eventually occur in about one-fifth of all cases.

2. SUBCLAVIAN STEAL SYNDROME

The subclavian steal syndrome results from subclavian or innominate artery stenosis that causes retrograde blood flow in the vertebral artery, with subsequent brainstem hypoperfusion. The degree of subclavian artery stenosis that will produce symptoms is quite variable, and a minor (40%) stenosis may cause the syndrome in some patients. A difference between blood pressures measured in the two arms is nearly always found, the average difference being a 45-mm Hg decrease in systolic pressure in the arm supplied by the stenotic vessel. In one series of cases, while syncope was described in 18% of patients, vertigo, diplopia, limb paresis and paresthesias, and ataxia were more common manifestations. Stroke resulting from this condition is rare. If this diagnosis is suspected, arteriography and subsequent surgical correction may be indicated.

3. MIGRAINE

Syncope occurs in 10% of migrainous patients during the headache, often upon rapid rising to a standing position, suggesting that loss of consciousness is due to orthostatic hypotension. In some patients, basilar migraine produces symptoms similar to those of basilar artery transient ischemic attacks. Antimigraine drug therapy is often effective in preventing attacks.

4. TAKAYASU'S DISEASE

Takayasu's disease (aortic arch syndrome, pulseless disease) is a panarteritis of the great vessels that is most common in Asian women. Symptoms of central nervous system hypoperfusion such as impaired vision, confusion, or syncope are often prominent. In one reported series, syncope was noted in 75% of patients, particularly following exercise, standing, or head movement. Physical examination reveals decreased or absent brachial pulses with low blood pressures in both arms. The erythrocyte sedimentation rate is moderately elevated during the acute stage. Hospitalization for evaluation and initiation of corticosteroid treatment is indicated.

5. CAROTID SINUS SYNCOPE

Carotid sinus syncope is uncommon. Men are affected twice as often as women, and most affected individuals are over 60 years of age. Drugs known to predispose to carotid sinus syncope include propranolol, digitalis, and methyldopa. Classically, pressure on the carotid sinus by a tight collar, a neck mass, enlarged cervical lymph nodes, or a tumor causes vagal stimulation, which inhibits the cardiac sinoatrial and atrioventricular nodes and reduces sympathetic vascular tone. The resultant bradycardia or systemic hypotension may then produce syncope; pure cardioinhibitory or vasodepressor syncope also occurs. The bradycardia can be abolished or prevented by administration of atropine.

Carotid sinus syncope may be mistakenly diagnosed when symptoms result from compression of a normal carotid artery contralateral to an occluded internal carotid. Under these circumstances, unilateral compression transiently interrupts the entire anterior cerebral circulation. Performing carotid sinus massage in an attempt to diagnose carotid sinus syncope in patients with carotid atherosclerotic disease produces a risk of distal embolization of atheromatous material.

MISCELLANEOUS CAUSES OF SYNCOPE

1. ORTHOSTATIC HYPOTENSION

Orthostatic hypotension occurs more often in men than in women and is most common in the sixth and seventh decades. It may, however, appear even in teenagers. Loss of consciousness usually occurs upon rapidly rising to a standing position, standing motionless for a prolonged period (especially following exercise), and standing after prolonged recumbency (especially in elderly patients).

Numerous conditions can produce orthostatic hypotension, which generally results from either reduced blood volume or autonomic nervous system dysfunction. The latter may be due to sympathetic drugs, autonomic neuropathy, or central nervous system disorders affecting sympathetic pathways in the hypothalamus, brainstem, or spinal cord. Two neurogenic causes of orthostatic hypotension deserve special consideration. Idiopathic orthostatic hypotension is associated mainly with the degeneration of postganglionic sympathetic neurons without other neuropathologic changes. In Shy-Drager syndrome, orthostatic hypotension appears to be related to degeneration of preganglionic sympathetic neurons; this occurs in combination with parkinsonian, pyramidal, cerebellar, or lower motor neuron signs.

The diagnosis of orthostatic hypotension is established by demonstrating a drop in blood pressure of at least 30 mm Hg systolic or 10 mm Hg diastolic when the patient changes from the lying to the standing position. In equivocal cases, tilt-table testing may be necessary. A detailed general physical and neurologic examination and laboratory studies (hematocrit, stool occult blood, serum glucose and electrolytes, FTA-ABS, nerve conduction studies) should be directed toward establishing the cause of the disorder.

Any medication that might be responsible should be discontinued if possible, and the patient should be instructed to stand up gradually, to elevate the head of the bed on blocks, and to use waist-high elasticized support hosiery. Other therapy is dictated by the specific cause of hypotension. The potent mineralocorticoid fludrocortisone has been effective in idiopathic cases and in diabetic patients in doses beginning with 0.1 mg/d orally and increased gradually, as necessary, up to 1 mg/d orally. Its mode of action is unclear, but its benefit may relate to increased responsiveness to circulating norepinephrine, as well as to an increased plasma volume. Side effects include recumbent hypertension, but to treat this compounds the primary problem of orthostasis.

2. HYPERVENTILATION SYNCOPE

Hyperventilation is a frequent cause of faintness or dizziness but rarely culminates in syncope. Common symptoms include lightheadedness, shortness of breath, circumoral numbness and tingling, and muscular twitching. Pathophysiologically, hypocapnia produces cerebral vasoconstriction and results in central nervous system hypoperfusion. Patients are usually between 20 and 40 years of age, and women are affected far more frequently than men. The disorder is usually benign, with anxiety a prominent precipitant, but serious cardiopulmonary causes of hyperventilation or subjective dyspnea must be excluded. Symptoms commonly occur in the lying position, which can be diagnostically helpful. Patients often report prolonged unconsciousness, but upon close questioning this rarely proves to be true. Hyperventilation at the examiner's request often reproduces the symptoms.

3. COUGH SYNCOPE

Cough syncope occurs chiefly in middle-aged men with chronic obstructive pulmonary disease but has also been reported in children. Coughing need not be prolonged and immediately precedes unconsciousness, which may occur while the patient is supine. Prodromal symptoms are absent, and the duration of unconsciousness is brief – often only a few seconds. Full recovery of consciousness occurs immediately. A history of similar episodes is common, and symp-

toms may be reproduced by having the patient cough on request. The cause may be a decrease in cerebral blood flow from increased intracranial pressure, which results from transmission of increased intrathoracic pressure to the intracranial compartment via the spinal fluid or venous connections. The condition is usually benign, and there is no specific treatment except for antitussive drugs such as dextromethorphan.

4. MICTURITION SYNCOPE

Micturition syncope occurs almost exclusively in men, probably because of the standing position for urination. Episodes can occur immediately before, during, or after micturition. They are more likely to occur at night following the prolonged recumbency of sleep and are due to peripheral pooling of blood plus a vagally induced bradycardia. Urination in a sitting position usually eliminates the symptoms.

5. GLOSSOPHARYNGEAL NEURALGIA

Glossopharyngeal neuralgia is a rare syndrome of intermittent, agonizing paroxysmal pain localized to the tonsillar pillar or occasionally to the external auditory meatus. The pain is triggered by contact with or movement of the tonsillar pillars, especially during swallowing or talking. Syncope occurs as a consequence of the activation of a glossopharyngealvagal reflex arc, producing a transient bradyarrhythmia with resultant cerebral hypoperfusion. Carbamazepine, 400-1000 mg/d orally, will prevent pain and bradycardia in most patients.

6. PSYCHOGENIC SYNCOPE

Psychogenic syncope is a diagnosis of exclusion and is often made erroneously. Suggestive features are lack of any prodrome, possible secondary gain, bizarre postures and movements, lack of pallor, and a prolonged period of apparent unresponsiveness. Psychogenic spells rarely occur when the patient is alone and they rarely are associated with incontinence or result in injury. Most patients are young or have a well-documented history of conversion disorder. Without such a history, diagnosis after the third decade is suspect. The EEG during psychogenic unconsciousness is normal, without the slowing that typically follows unconsciousness from a seizure. Caloric testing, which produces nystagmus in conscious patients, and tonic eye deviation in unconscious patients, can distinguish psychogenic unresponsiveness from coma caused by a metabolic or structural lesion.

MULTIPLE SCLEROSIS AND DEMYELINATING DISEASES

Multiple sclerosis (MS) is an inflammatory, demyelinating disease of the central nervous system (CNS). MS lesions, characterized by perivascular infiltration of monocytes and lymphocytes, appear as indurated areas in pathologic specimens; hence, the term "sclerosis in plaques."

MS is a dynamic disease, with almost constant lesion formation and a progressive clinical course leading to physical disability. For every 8-10 new lesions detected on magnetic resonance imaging (MRI), only one clinical manifestation typically can be demonstrated. Patients with relapsing remitting MS have an average of 20 new lesions per year and one or two clinical exacerbations.

With the advent of MRI, the ability to confirm the diagnosis of MS has improved dramatically. MRI characteristically shows lesions of high T2 signal intensity of variable location in the white matter of the brain, brain stem, optic nerves, or spinal cord. In typical cases, the lesions tend to occur in periventricular areas and may occur in the corpus callosum. Newer MRI techniques (eg, magnetization transfer, fluid attenuated inversion recovery [FLAIR], MR spectroscopy [MRS]) promise to yield important information regarding MS heterogeneity, prognosis, and treatment effects.

Despite intensive efforts at finding the source of the disease, no etiologic agent for MS has been identified. The disease presumably can be exacerbated by hormonal changes during the postpartum period. Some argue that MS could be a heterogeneous disorder triggered by several different environmental agents. In fact, only 1 of every 4 MS attacks is associated with a viral infection.

The disease can present in different forms, such as primary progressive, relapsing remitting, relapsing progressive, and secondary progressive phenotypes. Genetic susceptibility factors may play a role, as the disease is more common in Caucasian populations living in northern latitudes. This susceptibility may be part of a complex and heterogeneous group of factors that have an impact, along with environmental factors, on the initiation and maintenance of disease. In addition, migration to high-risk areas before age 15 years is known to increase the risk of developing MS, lending further support to the environmental factor hypothesis.

Pathophysiology

MS is characterized by perivenular infiltration of lymphocytes and macrophages in the parenchyma of the brain, brain stem, optic nerves, and spinal cord. Expression of adhesion molecules on the surface seems to underlie the ability of these inflammatory cells to penetrate the blood-brain barrier. The ele-

vated immunoglobulin G (IgG) level in the cerebrospinal fluid (CSF), which can be demonstrated by an oligoclonal band pattern on electrophoresis, suggests an important humoral (ie, B cell activation) component to MS. In fact, variable degrees of antibody-producing plasma cell infiltration have been demonstrated in MS lesions.

Molecular studies of the white matter plaque tissue have shown that interleukin (IL)-12, a potent pro-inflammatory substance, is expressed at high levels in early formed lesions.

- A molecule required to stimulate lymphocytes to release pro-inflammatory cytokines, B7-1, also is expressed at high levels in early MS plaques.
- Evidence exists of higher frequencies of activated myelin-reactive T cell clones in the circulation of patients with relapsing remitting MS and higher IL-12 production in immune cells of patients with progressive MS, when compared to healthy controls.
- The favorable clinical responses to the newer disease-modifying immunomodulatory agents (ie, interferon beta-1a and -1b, glatiramer acetate) suggest that these medications modify disease progression on the basis of their ability to counteract the pro-inflammatory phenotype of immune cells. However, MS is a complex and heterogeneous disease, and our understanding of the disease initiation mechanism and its wide clinical variability is limited.

Frequency

MS has a prevalence of nearly 350,000 cases in the United States alone. Every year, approximately 10,000 persons are newly diagnosed with MS. More than 1 million worldwide are affected. MS causes considerable disability in the working age group. People with MS usually die of complications rather than of MS itself, including recurrent infections (especially in bedridden patients). Patients with MS have an average life expectancy 7 years shorter than that of the general population. MS presents more often in populations of northern European ancestry. Whether disease severity also may be accounted for by racial differences is controversial. The concordance rate for MS is 20-40% among monozygotic twins, suggesting the presence of predisposing genetic factors of non-Mendelian inheritance. MS affects females more than males (1.6-2:1), but the basis for this difference is unknown. This ratio is even higher (3:1) among patients in whom onset of MS is before age 15 years or after age 50 years, suggesting a hormonal component to the disease process. Males have a greater tendency to develop primary progressive MS, while females tend to experience more relapses. MS most commonly afflicts people between the ages of 18 and 50 years, but any age group can be affected.

Clinical presentation

Attacks or exacerbations of MS are characterized by new symptoms that reflect CNS involvement. These symptoms typically are separated in time (eg, weeks, months or years) and in anatomical location (eg, one or more limbs, optic nerve, sensory symptoms). Recognizing that physical and cognitive disability in MS may occur in the absence of clinical exacerbations is important.

Patients who improve after acute attacks have relapsing remitting MS (RRMS). However, during the natural course of RRMS, approximately 75-85% of patients enter a stage referred to as secondary progressive MS (SPMS).

Patients with primary progressive MS (PPMS) tend to accumulate disability without interruption (ie, without remissions). Some of these patients first present with weakness of only one limb, which gradually progresses to involve other limbs and culminates in total paralysis. Patients with PPMS typically respond poorly to the current therapeutic options for MS, accumulate disability faster than other patients, and tend to have more weakness of the legs as well as incontinence (a reflection of greater spinal cord involvement).

Patients with PPMS tend to have more involvement of the spinal cord by demyelinating plaques. These cases must be differentiated from SPMS.

Patients who have RRMS but accumulate disability between and during attacks can be defined as having relapsing progressive disease (RPMS), a term not widely used by neurologists.

Although most patients have a wide range of symptoms from lesions in different areas of the brain and spinal cord, others may present with predominantly visual, cognitive, or cerebellar symptoms.

Patients with MS are now thought to reach a clinical threshold (itself a reflection of immune system dysfunction and axonal involvement), after which deterioration occurs in a continuous course and more ominous MRI signs become apparent (eg, T1 hypointensities, brain atrophy). These T1 "holes" and signs of brain or spinal cord atrophy are a manifestation of a neurodegenerative process, indicating that MS is not only an inflammatory disease. The history will reflect these processes, as patients often report short-term memory problems, difficulty executing sequential tasks, or visuospatial disturbances.

Use of the term "benign MS" should be discouraged, since practically all patients have relentless progression of the disease, even in the absence of clinical attacks. Not uncommonly, detailed examination of a patient with so-called "benign MS" encounters clear evidence of short-term memory difficulties, cognitive dysfunction, or brain atrophy on MRI of the head. In the author's view, the use of the term "benign MS" leads to false expectations of disease outcome by the patients and their relatives, improper counseling, and inappropriate delay of treatment with disease-modifying drugs.

Patients with MS tend to experience variable degrees of fatigue. This symptom typically is described as either physical exhaustion or mental/cognitive slowing. It must be differentiated from depression (which may, however, coex-

ist), lack of sleep, and exertional exhaustion due to disability. Patients may feel particularly fatigued after taking a hot shower or after strenuous activity in heated environments. Heat exposure also may lead to episodes of optic nerve dysfunction (ie, Uhthoff phenomenon), the mechanisms of which remain poorly understood.

Multiple sclerosis may present in an acute and clinically fulminant form (termed Marburg variant of MS) or may present with concomitant optic nerve involvement and necrotizing myelopathy (ie, neuromyelitis optica or Devic disease, considered by some to be an MS variant). However, MS must be distinguished from other neuroinflammatory disorders, including acute disseminated encephalomyelitis (ADEM), Schilder disease, and Baly concentric sclerosis.

- ADEM is considered an isolated postinfectious or postvaccinial autoimmune attack on the CNS that leads to diffuse demyelination. It is often devastating, and occasionally has a fulminant hemorrhagic component (in which case it is termed acute hemorrhagic encephalomyelitis or leukoencephalitis of Weston Hurst).
- Schilder disease is characterized in children and young adolescents by massive demyelination, presenting often as asymmetrical foci (often the size of an entire lobe) in the white matter by MRI, and presenting with a malignant course (ie, deterioration over months or a few years with cortical blindness, hemiplegia, or paraplegia). Some patients, however, may respond to steroids and immunosuppressive therapy.
- Baly concentric sclerosis is considered by some authors to be a variant of Schilder disease, with MRI lesions showing a characteristic alternating pattern of spared and damaged white matter that suggests progression of the disease process from the ventricles outward. Baly disease often is associated with a more inflammatory CSF and a more fulminant progression than typical MS.

MS may present in various forms. Some patients have a predominance of cognitive changes, while others present with prominent ataxia, hemiparesis or paraparesis, depression, or visual symptoms. Bipolar disorder and frank dementia may appear late in the disease course, but sometimes are found at the time of initial diagnosis. Symptoms can be exacerbated by intercurrent illness, including viral or bacterial upper respiratory or urinary tract infections. Trauma has no impact on disease exacerbation. The impact of emotional stress on exacerbations is probably minimal and remains controversial.

Optic neuritis presents clinically as orbital pain, at rest or during eye movement, and loss of vision. Patients may complain of "patchy loss of vision," and upon examination, a cecocentral scotoma and an afferent pupillary defect may be found. Patients may experience color desaturation even with normal visual acuity, usually manifested as the perception of red color as different shades of orange or gray.

Patients with MS may present with facial palsies or trigeminal neuralgia. In fact, the presence of bilateral facial weakness or trigeminal neuralgia strongly suggests the diagnosis of MS. Facial myokymia also may be a presenting symptom. Nystagmus (direction-changing) and internuclear ophthalmoplegia signs are other manifestations.

Painful limb syndromes are important to recognize. Commonly, patients complain of numbness or tingling in one or more limbs, variable weakness, or sensory level-related symptoms. Some have difficulty describing weakness or numbness, as these symptoms are obscured by incapacitating fatigue.

Episodes of central (as opposed to peripheral) vertigo are not uncommon. The nystagmus accompanying central vertigo has a rapid onset, does not fatigue easily, and changes with direction of gaze. CNS vertigo usually is accompanied by other complaints that can be directly attributed to brainstem or cerebellar pathway involvement (eg, diplopia, dysarthria).

An often overlooked manifestation of MS is the pseudobulbar affect, whereby patients have difficulty controlling their emotions (laughing, crying) and are perceived to act inappropriately by co-workers or friends. Behavioral/cognitive symptoms also may include social disinhibition, dementia, or depression. A greater tendency for attempting and committing suicide in MS is not related exclusively to a reactive depression, since this tendency is higher than that of patients with other devastating neurological disorders such as chronic inflammatory demyelinating polyradiculopathy (CIDP). The neurologist should be aware that patients with conversion reactions and inappropriate affect, such as "la belle indifference," may on occasion have an underlying organic illness such as MS.

Urinary retention and incontinence are common. Bowel habit changes may occur, but bowel incontinence is less frequent.

Sexual dysfunction affects the great majority of patients with MS and includes symptoms such as lack of desire, erectile dysfunction, impaired sexual responsiveness, premature ejaculation, impaired genital sensation, or inability to physically interact with the partner due to painful leg adductor muscle spasms.

The Kurtzke Expanded Disability Status Scale (EDSS) is used as a measure of disease progression by assigning a severity score (0-10) to the patient's clinical status. Although the scale does not correspond linearly to common progression points for many patients, its widespread use and ease of implementation allow its utilization as a standardization measure for clinical trials (Kurtzke, 1983).

Causes

The cause of MS is unknown. An environmental agent (eg, virus, bacteria, chemicals) has been hypothesized to act in concert with a specific genetic predisposition (ie, a set of genes or polymorphisms) to result in immune dysfunc-

tion. For instance, different variants of genes normally found in the general population, commonly referred to as polymorphisms, may lead to different gradations of cellular expression of those genes and, thus, of the proteins that they encode. Therefore, an individual with a polymorphism within the promoter region of a gene that is involved in immune reactivity may generate an exaggerated response (eg, elevated gene expression of a pro-inflammatory gene) to a given antigen, leading to uncontrolled immune cell proliferation and autoimmunity.

Research on cytokine gene polymorphisms in MS is just beginning but promises to yield important clues about the pathogenesis of this disease. Genes encoding antigen presentation molecules such as the human leukocyte (HLA) antigens are highly polymorphic and have been shown to play a role in mediating MS susceptibility. For instance, MS has been associated, although not exclusively, with the HLA-DR2 allele, and linkage of MS to genetic regions where the HLA genes lie also suggests a component of genetic predisposition.

Other molecules involved in activation of T and B cells have been implicated in MS. For instance, the co-stimulatory molecule B7-1, necessary for activation of T cells as a second signal to antigen presentation, has been found to be elevated in early MS lesions, suggesting a triggering role for inflammation within the CNS. Other factors elevated in MS brain tissues include the pro-inflammatory interferon gamma and the pro-demyelinative tumor necrosis factor alpha molecule. In addition, interactions between molecules on the surface of B and T cells, such as CD40 and CD40 ligand, may mediate elevated levels of IL-12 (a pro-inflammatory cytokine) in the circulation of patients with MS.

The molecular mimicry hypothesis refers to the possibility that peripheral blood T cells may become activated to attack a foreign antigen, then erroneously direct their attack toward brain proteins that share similar protein epitopes.

Others support the hypothesis that a virus may infect the immune system, activating self-reactive T cells (myelin reactive) that would otherwise remain quiescent.

Different Diagnosis

Acute Disseminated Encephalomyelitis
Atypical Facial Pain
Brainstem Gliomas
Central Pontine Myelinolysis
Essential Tremor
HIV-1 Associated CNS Complications
HIV-1 Associated Opportunistic Infections: PML
HIV-1 Associated Opportunistic Neoplasms: CNS Lymphoma
HIV-1 Associated Vacuolar Myelopathy
HIV-1 Encephalopathy and AIDS Dementia Complex

Hemifacial Spasm
Inherited Metabolic Disorders
Lyme Disease
Lysosomal Storage Disease
Metabolic Disease & Stroke: MELAS
Myokymia
Paraneoplastic Encephalomyelitis
Primary CNS Lymphoma
Primary Lateral Sclerosis
Spinal Cord Infarction
Sudden Visual Loss

Workout

Cerebrospinal fluid examination

Oligoclonal bands are distinct electrophoretic patterns that reflect substantial elevation of IgG produced by a restricted set of plasma cells and are demonstrated in CSF samples of approximately 85% of patients with MS.

Glucose level is usually normal. Protein level can be normal or slightly elevated. WBC count can be slightly to moderately elevated (6-40 x 10^9/L) but is usually <5 (predominantly mononuclear cells).

IgG index usually is elevated. This index is derived from the following formula: IgG Index= $[IgG_{CSF}/albumin_{CSF}]/[IgG_{serum}/albumin_{serum}]$
Although the sensitivity of measurements may vary among various laboratories, a typically normal CSF IgG is <4.7 mg/dL (less than 12% of serum protein), and the normal IgG index is <0.77. Most patients with MS have an elevated IgG index (>1.7).

Myelin basic protein (MBP) is a major component of myelin and may be elevated in the CSF of patients with MS. However, its clinical utility as a marker of disease activity or progression is limited.

Blood tests

Patients with MS and atypical features initially should be tested for B_{12} and folate levels or antinuclear antibody (ANA) titers. For instance, rapid cognitive deterioration or evidence of subacute combined degeneration of the spinal cord by clinical examination should prompt testing for folate and B_{12} levels.

Anti-cardiolipin antibodies should be tested in patients with evidence of blood dyscrasia or in women with unexplained miscarriages.

An elevated erythrocyte sedimentation rate (ESR) and positive titers of rheumatoid factor (RF) should help identify the presence of a vasculitic disorder that may be mimicking MS.

If patients come from an endemic region for Lyme disease or have been exposed to tick bites, the physician should check Lyme titers. Evaluation by a

rheumatologist should be sought if positive Lyme or ANA titer, elevated ESR, or evidence of vasculitis is uncovered.

If clinical suspicion for a peripheral neuropathy arises, electrophysiological studies and blood tests for metabolic or toxic neuropathies should be done.

Imaging Studies

MRI of head or spine, with and without gadolinium, should be performed according to clinical suspicion for lesion localization.

Typical MS lesions appear as T2 hyperintensities in the periventricular regions; they have an ovoid appearance with their largest axis oriented perpendicular to the ventricular surface; they involve only the white matter, and several arise from the corpus callosum. This characteristic configuration has been demonstrated in pathologic specimens and sometimes is referred to as "Dawson fingers" on the basis of neuropathologic work done in 1916 at the University of Edinburgh by James Dawson, who identified the perivascular distribution of inflammatory cells and the resulting fingerlike appearance of affected veins and venules in MS brain tissues.

The most common infratentorial locations for plaque formation are the surface of the pons, the cerebellar peduncles, and white matter regions adjacent to the fourth ventricle.

Lesions that enhance with gadolinium are thought to reflect active disease, as enhancement may correspond to breakdown of the blood-brain barrier from an ongoing subacute inflammatory process (few days to a few weeks). Usually a combination of enhancing and non-enhancing lesions is seen, reflecting the chronicity of the demyelinating process.

In a patient with a first clinical attack who presents with numerous (ie, >10) lesions by MRI, the presence of gadolinium enhancement in most or all the lesions is highly suggestive of ADEM; it is less likely to represent an extremely aggressive presentation of MS. A history of recent exposure to a vaccine or viral illness may be helpful in supporting the diagnosis of ADEM. However, note that exceptions occur and some patients with MS present with a fulminant and active demyelinative disease form from the onset.

Hypointensity of lesions in T1 images may reflect some degree of axonal damage or more chronic tissue damage resulting in gliosis. The clinician should attempt to correlate lesions with high T2 signal intensity with their corresponding T1 images to assess chronicity. Although a lesion may appear old (low T1), it may exhibit a ringlike enhancement around the hypointense region after gadolinium, suggesting that even old lesions may have a component of active inflammation, especially at the advancing edge of lesion formation. Additionally, a new lesion may present with T1 hypointensity, reflecting marked edema. Lesions range from a few millimeters to more than a centimeter in diameter with occasional large, rounded, tumorlike lesions. The latter are seen as areas of pronounced gliosis and demyelination on pathologic inspection.

The application of modern MRI techniques to detection and characterization of early lesions is changing rapidly. Recent MRI techniques such as FLAIR have increased the ability to detect demyelinating lesions due to MS. A disadvantage of FLAIR remains the less-than-optimal visualization of the posterior fossa. Other recent techniques such as fast FLAIR and fast spin-echo may increase the sensitivity of prediction for diagnostic and prognostic purposes. Magnetization transfer ratio (MTR) abnormalities may precede the appearance of T2-weighted and proton-density high-intensity lesions. Finally, MRS, which can identify neutral fat, helps identify the appearance of myelin breakdown products that result from the active inflammatory response. Axonal loss is identified by the detection of reduced levels of *N*-acetylaspartate (NAA), a marker of neuronal integrity/metabolism, on MRS.

Other Tests

Evoked potential testing (visual, auditory, or somatosensory) is especially helpful in 1) detecting clinically silent lesions, and 2) documenting an organic basis for vague complaints. The most sensitive are the visual evoked potentials (50-80% sensitivity), followed by the somatosensory potentials (50-70% sensitivity).

Histologic Findings

Histopathologic examination reveals that MS lesions are caused by perivenular infiltration of lymphocytes (most of which are CD4+ T cells) and macrophages. Some lesions may have more infiltration by B cells. In fact, recent immunostaining reports by Lucchinetti et al show that MS lesions have considerable heterogeneity of microscopic appearance, with some lesions exhibiting oligodendrocyte apoptosis and others marked complement and antibody presence. Luxol fast blue stains (which stain myelin with an intense blue) reveal demyelinated areas as pale and confluent patches, with variable degrees of associated inflammation. Transected axons may be found in chronic and sometimes in acute MS lesions, as demonstrated by recent studies by Trapp and collaborators; these recent studies have helped refocus neurologists' attention to the issue of axonal loss in MS. Expression of interferon gamma, IL-12, and B7 molecules is increased, especially in early MS lesions; this reflects the inflammatory nature of plaque formation.

Treatment

Medical Care

Patients with MS have multiple needs, and the neurologist should be receptive and cooperative and try to allay fears, facilitate access to rehabilitation and orthotic equipment and home evaluations, and solve transportation issues. Bone densitometry studies are indicated for patients with MS who have received

long-term corticosteroid treatment or are at higher osteoporosis risk from menopause or chronic immobility.

Patients with more advanced forms of the disease who have lost all family support, are separated from their spouses, require constant psychiatric and nursing assistance, and are unable to walk are not rare. These patients create a challenge for the physician who is not trained in handling these demanding (administrative or ancillary) aspects of medical care.

The physician should not underestimate the impact of fatigue symptoms on the patient's daily activities. Treatment with amantadine (Symmetrel) or modafinil (Provigil) should be attempted if no contraindications exist. Pemoline should be used with caution for the treatment of fatigue because of reports of rare fatal liver damage events in patients taking this medication.

Patients who have progressed beyond EDSS scores of 5.5-6 tend to respond poorly to the current treatments.

The impact of this disease on quality of life is reflected in the high suicide rate (7.5 times higher than in the general population). As already stated, however, reactive depression by itself does not fully account for this higher suicide incidence. Many believe that the accumulation of lesions in the brain eventually has an impact on mood.

Thus, preventing disease progression by using available medications is imperative in MS treatment, especially for patients who have been diagnosed early and probably will respond to treatment.

Prevent disease progression by using the "ABC" immunomodulatory drugs (ie, interferon beta-1a [Avonex], interferon beta-1b [Betaseron], and glatiramer acetate [Copaxone]). These 3 medications have been approved by the US FDA and are currently used in the United States as therapies for MS. Although no specifically designed large-scale studies have been completed to date to compare the relative benefits of each drug, as a rule of thumb the ABC medications tend to decrease the rate of appearance of new MRI lesions by approximately one third.

Interferon beta-1b (8 MIU every other day) was shown in a 2-year, double-blind, placebo-controlled trial of 372 patients with RRMS to decrease the frequency of relapses from 1.27/year to 0.84/year, a 34% reduction in the relapse rate compared to placebo. Five-year follow-up data show that disease progression rate was 35% in the interferon beta-1b group and 46% in the placebo group. A 30% decrease in the yearly exacerbation rate in the treated group over 5 years also was demonstrated. While the placebo group had a median MRI lesion burden of 30.2% over 5 years, no significant increase (3.6%) was detected in the patients treated with interferon beta-1b. Interferon beta-1b is of benefit in delaying disability in early SPMS.

Interferon beta-1a was studied in a double-blind placebo-controlled study in 301 patients with RRMS receiving weekly intramuscular (IM) injections of 6 million units (30 micrograms). Over 2 years the annual exacerbation (ie, relapse)

rate was 0.90 in the placebo group and 0.61 in the Avonex-treated group, a 29% reduction. At 2 years, the mean MRI lesion volume was 122.4 in the placebo group and 74.1 in the Avonex-treated group. The mean number of MRI enhancing lesions over 2 years was 1.65 in the placebo group and 0.80 in the Avonex-treated group. By the end of 104 weeks, the proportion of patients progressing was 34.9% in the placebo group and 21.9% in the Avonex group. Also, 22% of patients on treatment developed neutralizing antibodies.

Recent results suggest that Avonex may help delay brain atrophy and cognitive decline in patients with MS, but more long-term data are needed to assess the significance of its clinical impact.

Interferon beta-1a was shown by the CHAMPS and ETOMS trials to delay the onset of disease (ie, recurrent attacks) if administered to patients after an isolated demyelination event. Considerable controversy exists regarding whether the delay in onset of new attacks by these drugs ultimately has a long-term impact on neurodegeneration and disability; these issues need to be addressed in future trials.

Controversy has also existed regarding the eventual clinical impact (positive or negative) of raising the dose of these medications to maximally tolerated levels — studies (INCOMIN trial study group) that compared the effects of interferon beta-1a administered subcutaneously (SC) and interferon beta-1a administered IM suggest that higher and more frequent doses correlate with higher efficacy. The EVIDENCE trial, which compared interferon beta-1a SC (Rebif) to interferon beta-1a IM, also found that higher dosing and more frequent administration lead to more efficacy. However, in some patients, higher doses may increase the chance of generating neutralizing antibodies. Studies of combinations of interferons with drugs such as methotrexate and glatiramer acetate are also underway.

Glatiramer acetate showed positive effects in a large randomized double-blind trial in 251 patients with RRMS. Patients on Copaxone had a 2-year relapse rate of 1.19, while patients on placebo had a rate of 1.68. The relapse rate reduction was 29% over 2 years for patients on Copaxone. Extension data show that over 140 weeks, 21.6% of patients treated with Copaxone worsened, while 41% of those on placebo worsened. Recent results of an 18-month study examining the impact of Copaxone on MRI outcome show a 35% reduction in the number of new T2 lesions.

Acute exacerbations. No highly effective treatment is currently available to counteract MS attacks after their onset. The most widely used treatment is intravenous (IV) methylprednisolone, 1 g IV qd for 3-5 days. This medication may help expedite the timing of recovery but will not affect the actual degree of recovery.

High-dose IV steroids may work more effectively than oral steroids for the acute attack, and home IV therapy is recommended if the patient does not

require hospitalization. Alternatively, high-dose oral methylprednisolone should be used, when feasible.

Secondary progressive forms. These patients may be treated with Betaseron, especially when the clinical course reflects an early phase of progression (EDSS score <6). Betaseron is also effective for RRMS.

Mitoxantrone is approved in North America and Europe for use in patients with MS. Patients on mitoxantrone need to be monitored with echocardiograms prior to and during treatment, as the drug carries a risk of cardiomyopathy.

No head-to-head study has yet compared the efficacy of mitoxantrone and cyclophosphamide (Cytoxan) in large numbers of patients. When studied individually, mitoxantrone seems effective for all ages tested. The data on cyclophosphamide, in contrast, indicate that this drug may be more helpful to male patients younger than 40 years. Controversy exists whether patients with dramatic and rapid progression of disease (regardless of the type and timing of MS) should be treated with immunosuppressive agents to try and arrest the ongoing inflammatory cascade.

Azathioprine and methotrexate also may be used as immunosuppressive treatments for MS, but these drugs should not substitute for ABC drugs as first-line agents in newly diagnosed RRMS. They are considered less suppressive than mitoxantrone or cyclophosphamide, and are being considered increasingly as combination partners for the ABC drugs.

Surgical Care

Surgical procedures that relate to MS are directed primarily at alleviating symptoms such as dysphagia, significant limb spasticity or contractures, or severe neuropathic pain. Measures include gastrojejunal tube placement, adductor leg muscle tendon release, and rhizotomy, respectively. Intrathecal pumps for delivery of antispasticity medications (eg, baclofen) can be implanted surgically. Penile prostheses are an alternative for patients with erectile dysfunction that does not respond to medical management.

Consultations

Because of the disseminated CNS involvement, patients with MS may require multiple consultations to rule out other causes for their symptoms. For instance, patients with dysphonia may need an evaluation by an otolaryngologist (ie, ear, nose, and throat specialist) to rule out laryngeal lesions unrelated to MS. In addition, having MS does not exclude the possibility of concomitant peripheral neuropathy or other illnesses that may cause pain.

Listed below are the most common consultant services involved in referrals from an MS clinic (Otolaryngology, Neuropsychology, Ophthalmology, Physical therapy and rehabilitation, Psychiatry, Gastroenterology, Urology). Gastric tube (G-tube) placement for feeding in advanced cases is an example. Urologic consultation might be warranted to help assess and treat incontinence. Neuropsychological evaluation, especially in patients with primary cognitive in-

volvement, is advisable so that a baseline assessment for future reference can be obtained.

Diet

No specific dietary restrictions apply to patients with MS; patients are encouraged to eat a balanced diet. Oral intake of calcium and multivitamin supplements is encouraged, as are adequate vitamin D sources. Although more studies are needed, recent observations suggest a role for vitamin D-related pathways in MS susceptibility.

Activity

Patients are encouraged to exercise regularly. Strenuous exercise and excessive exposure to heat and or physical exhaustion probably should be avoided; however, no studies have addressed this issue comprehensively in patients with MS. Patients with MS should avoid exposure to hot showers or saunas, as increased body temperature has been associated with MS exacerbations. Sunlight by itself is not considered to be deleterious, but excessive exposure may mimic the effects seen with hot showers or high temperatures.

Medication

In the past 5 years, neuroimmunology has witnessed an unprecedented expansion in treatment options for CNS autoimmunity. Multiple MS drug trials are ongoing throughout the world, with many disappointments but occasional positive results.

Drugs for MS discussed in this article have been evaluated in clinical trials that measure one or several of the following primary endpoints:

- Delay in progression to disability
- Reduction in relapse rate
- Increase in the number of relapse-free patients
- Increase in the time to first relapse
- Decreased MRI lesion burden, atrophy, and "T1 holes," or presence of new lesions

Patients should be educated and warned that these medications are preventive, not curative. Patients need to understand that mild sensory attacks may not warrant acute intervention with corticosteroids. Treatment of acute attacks should be reserved for functionally disabling symptoms and findings.

Therapeutic approaches such as combination therapy, intravenous immunoglobulin (IVIg), hormonal treatment, bone marrow transplantation, and plasmapheresis are not discussed here, as larger trials are needed for definitive recommendations. Combination therapy may be beneficial for some patients, however, and this practice may become commonplace within a few years. Treatments that can be used as combination partners include methotrexate, azathioprine, IVIg, and plasmapheresis. Briefly, treatments of choice include the following:

- Depression – Fluoxetine (Prozac), sertraline (Zoloft), amitriptyline (Elavil)
- Spasticity – Baclofen, tizanidine, dantrolene, diazepam (Valium), intrathecal baclofen delivered via programmable pump
- Painful tonic spasms – Baclofen, carbamazepine (Tegretol), gabapentin (Neurontin), phenytoin
- Fatigue – Amantadine, fluoxetine, methylphenidate (Ritalin), pemoline, selegiline, modafinil
- Urinary dysfunction – Propantheline bromide (Pro-Banthine), tolterodine tartrate, oxybutynin (Ditropan), imipramine (Tofranil); intermittent self-catheterization
- Tremors/ataxia – Clonazepam (Klonopin), primidone (Mysoline), propranolol (Inderal), gabapentin; weighted bracelets
- Erectile dysfunction – Sildenafil (Viagra), alprostadil (Muse), intracorporeal papaverine (not FDA approved), penile prostheses. Note that baclofen, fluoxetine, diazepam, and amitriptyline may contribute to sexual dysfunction (eg, decreased libido, erectile dysfunction, abnormal ejaculation).

Injection site reactions seen with the ABC (Avonex, Betaseron, Copaxone) drugs can be minimized by applying a topical steroid at the intended site a few hours prior to administration of the drug. These reactions include mild to severe erythema, skin induration or necrosis, and tissue loss or fibrosis, and may be complicated by superimposed bacterial infection.

Flu-like symptoms (commonly experienced with Avonex and Betaseron) can be minimized by taking over-the-counter acetaminophen or ibuprofen 3-4 hours prior and 3-4 hours following the injection.

Acute exacerbations that lead to constant pain or to physical impairment may be treated with IV methylprednisolone. If available, alternative high-dose oral methylprednisolone treatment may circumvent the need for hospitalization.

Follow up

Prevention

Patients must understand that the ABC immunomodulatory drugs are preventive, not curative. Early treatment is thus essential. Patients should avoid exposure to extreme heat. The impact of stress on MS exacerbations is thought to be minimal or noncontributory, and trauma has absolutely no impact on the disease course.

Complications

Complications in patients with MS include the following: Adverse drug reactions; Rare cases in which large, tumorlike demyelinating lesions necessitate brain biopsy to rule out malignancy. For bedridden patients, preventive meas-

ures regarding decubitus ulcers, atelectasis, pneumonia, and aspiration should be addressed.

Seizures are rare in MS but may occur at a higher rate than in the general population. Patients with seizures who work in conditions of high risk for self-injury (eg, operating heavy machinery) should exercise caution, taking into account specific state laws. This also pertains to driving a motor vehicle.

Patients with ataxia and weakness are at increased risk of falls and personal injury; the physician should recognize these patients early and provide any needed assistance.

Prognosis

If untreated, more than 30% of patients with MS will develop significant physical disability within 20-25 years from onset. This prognosis is changing for these patients with the advent of new treatments. Male patients with PPMS have the worst prognosis, responding less favorably to treatment and rapidly accumulating disability. The higher incidence of spinal cord lesions in PPMS is also a factor in the rapid development of disability. Fewer than 5-10% of patients have the benign MS phenotype, in which no significant physical disability accumulates despite several decades passing since onset (sometimes in spite of multiple new lesions by MRI). Detailed examination of these patients in many instances reveals some degree of cognitive deterioration. The physician should remind patients that early treatment with some agents may help counteract the progressive brain atrophy seen on MRI.

Medical/Legal Pitfalls

Treatment of "presumed MS" is not indicated. The neurologist should have a fairly reasonable diagnosis based on history, clinical examination, and MRI findings. Treatment based on a suspected diagnosis can lead to unnecessary emotional and financial costs and should be avoided. Results of the CHAMPS trial suggest that interferon beta-1a treatment of patients with a head MRI highly suggestive of advanced MS and an isolated clinical attack leads to some degree of protection from a second attack.

A common misconception is that any attack of demyelination means a diagnosis of acute MS and its implications for management. If a patient has the first attack of demyelination, the physician should not rush to diagnose MS. Postinfectious demyelination or other diseases that mimic MS should be considered carefully. Follow-up should be performed to ascertain whether the episode was self-limited. Although the CHAMPS and other trials suggest a benefit from early treatment, therapy for isolated demyelinating episodes with ABC medications has not yet become standard practice. The new McDonald diagnostic criteria are helpful in the decision to treat patients early during the course of MS.

Clinicians who specialize in MS commonly see patients referred for multiple, ill-defined, vague complaints who had recent head or spine MRIs in which T2 hyperintense lesions have been demonstrated. Careful questioning reveals that symptoms have been stereotyped and vague or do not truly qualify as exac-

erbations (eg, scintillating scotomas in a patient who also admits to concomitant migraines; symptoms consistent with carpal tunnel syndrome). A history of meningoencephalitis during childhood occasionally emerges and an explanation for the lesions may become obvious.

A third common problem is the presence of small T2 hyperintensities, typically referred to as "unidentified bright objects" (UBOs) by neuroradiologists. These nonspecific lesions are present to a large degree in the general population, and clinical correlation (ie, a high degree of suspicion based on clinical evidence) becomes important in the diagnosis. The neurologist seeking to confirm MS should look for sites of involvement that are rare localities for UBOs (eg, corpus callosum or throughout the spinal cord).

Special Concerns

For the patient with MS who wants to become pregnant, ABC drugs should be discontinued. If the patient becomes pregnant during treatment, the drug should be discontinued immediately. The treatment can be resumed a few weeks after delivery or after the patient finishes her period of lactation.

ACUTE DISSEMINATED ENCEPHALOMYELITIS

This occurs as a single episode of neurologic symptoms and signs that develop over a few days in association with a viral infection, especially measles or chickenpox. The neurologic deficit resolves, at least in part, over the succeeding few weeks. Pathologically, perivascular areas of demyelination are scattered throughout the brain and spinal cord, with an associated inflammatory reaction. A similar disorder may also occur independently, with no apparent infection; it may then represent the initial manifestation of multiple sclerosis.

The initial symptoms often consist of headache, fever, and confusion; seizures may also occur, and examination reveals signs of meningeal irritation. Flaccid weakness and sensory disturbance of the legs, extensor plantar responses, and urinary retention are common manifestations of cord involvement. Other neurologic signs may indicate involvement of the optic nerves, cerebral hemispheres, brainstem, or cerebellum.

Examination of the CSF may show an increased mononuclear cell count, with normal protein and glucose concentrations.

Corticosteroids are often prescribed, but there is little evidence of benefit. A mortality rate of 5-30% is reported, and survivors often have severe residual deficits.

AMYOTROPHIC LATERAL SCLEROSIS

Clinical features

Amyotrophic lateral sclerosis is the most feared motor neuron disease of adults, usually causing death within a few years. The first symptoms generally appear in the limbs but are bulbar in a quarter. Definite diagnosis requires the presence of both upper and lower motor neuron signs in the bulbar, arm, and leg musculature, with clear evidence of progression. But earlier on, particularly at the time of initial presentation, the disease is often more focal, only affecting one of these three regions of the body musculature.

Bulbar involvement causes dysphagia, drooling of saliva, dysphonia, or inhalation of foodstuffs due to varying combinations of weakness of the tongue, pharynx, or larynx. Lower motor neuron degeneration affecting the tongue shows as atrophy, fasciculation, and weakness. The tongue should be observed resting in the floor of the mouth, since attempts at protrusion produce pseudo-fasciculations in many normal people. Less frequently, weakness of the facial or trigeminal muscles causes leakage from the mouth or difficulty in chewing, respectively. Predominantly upper motor neuron lesions cause spasticity of the tongue and dysarthria, resulting in 'hot potato speech'. Such patients may show other evidence of a pseudobulbar palsy, such as a brisk jaw jerk or incontinence of emotional expression, with bouts of laughter or tearfulness. Eventually these bulbar symptoms lead to anarthria, aphagia, choking, and a'spiration. Death eventually results from malnutrition, unless alternative routes for feeding are established, or from respiratory failure, asphyxiation, or pneumonia.

The early symptoms of limb muscle denervation are usually cramps and fatigue, associated with observable fasciculations. Frequently such symptoms are ignored until symptomatic weakness and wasting of one hand or foot develops. Wasted small hand muscles or a foot drop are common early features. It is less common for proximal muscles, such as the shoulders, to be involved initially. Usually this first symptomatic limb remains that most severely affected until late in the disease. In the early stages of monomelic involvement, the patient may be investigated for alternative diagnoses, such as focal compressive neuropathy or a root lesion. However, clinical or electrophysiological evidence of denervation in muscles of other limbs is often detectable even in the very early stages. Over months, obvious weakness spreads to the opposite limb and eventually to remaining limbs and to the bulbar musculature. Eventually the patient becomes wheelchair- or bedbound, or unable to use the arms for grooming or feeding.

It is rare for spastic weakness due to upper motor neuron loss to be the dominant early symptom in the limbs. None the less, signs of upper motor neuron involvement, such as extensor plan tars, hyperreflexia, or spastic catches, are

often detectable early on. They are particularly valuable diagnostically if they coexist in a muscle, or a part of a limb, also affected by obvious lower motor neuron degeneration. In general, the tendon reflexes are retained until a muscle is almost completely denervated or the uncommon complication of fibrous replacement has supervened. An extensor plantar response cannot be elicited in severe extensor hallucis longus denervation, thereby sometimes masking the upper motor neuron involvement so necessary for diagnosing amyotrophic lateral sclerosis.

Respiratory muscle failure usually occurs in the wake of noteworthy bulbar muscle failure. Early and selective diaphragm involvement may occur in amyotrophic lateral sclerosis, occasionally as the presenting feature, and often merits ventilatory assistance in such cases. Exertional dyspnoea, orthopnoea, or difficulty in coughing out chest secretions are the common symptoms. Less commonly symptoms such as concentration difficulty, headache, or giddiness occur from carbon dioxide retention due to ventilatory failure. Diaphragm weakness is signalled by orthopnoea, and the forced vital capacity is lower when lying down compared to standing, because the weight of the liver no longer aids diaphragm descent when supine. Less frequently, respiratory symptoms are due to intercostal muscle weakness which may be associated with severe weakness of other axial muscles. If there is weakness of neck extension the chin drops onto the sternum with resultant dysphagia, dysarthria, and visual difficulties. Weakness of the abdominal wall leads to distension, difficulty in coughing powerfully, and inability to build up intra-abdominal pressure for defecation.

Other neuronal systems apart from motor neurons are commonly involved in amyotrophic lateral sclerosis, although generally subclinically. Paraesthesia or other short-lived minor somatosensory phenomena are noted in the early stages in up to 10 per cent of patients. Longitudinal electrophysiological studies show progressive loss of sensory nerve fibre function during the course of the disease, but none the less sensorynerve action potentials usually remain within the normal range. Autopsy studies show loss of spinocerebellar tract neurons from Clarke's nucleus, but one can only conclude that any corresponding clinical effects are overshadowed by the more severe limb weakness. Neuropsychological and positron emission tomography studies show impairments of cognitive function in up to 50 per cent of patients. However, these are rarely sufficient to produce thought deficits of everyday significance, nor indeed to blunt the patient's distressing awareness of being imprisoned within a body that can no longer move. Occasionally, rapidly progressive dementia occurs in association with motor neuron disease; or Parkinsonian features may develop simultaneously.

Micturition, defecation, and sexual function are not affected in amyotrophic lateral sclerosis, except in so far that trunk and limb muscle weakness may make such activities awkward or impractical. Despite this evidence of other neuronal involvement on detailed investigation, as a general rule, any clear clinical

evidence of neuronal involvement outside the motor system should raise questions about the validity of a diagnosis of amyotrophic lateral sclerosis.

Differential diagnosis and investigation

The diagnosis of amyotrophic lateral sclerosis is usually depressingly obvious on simple clinical grounds by the time the patient sees a neurologist, and often nothing needs to be considered in the differential diagnosis. The usual diagnostic problem lies in differentiating amyotrophic lateral sclerosis from other motor neuron diseases, polyneuropathies, or myopathies. Electrophysiological investigation is necessary to confirm denervation rather than myopathy, to detect clinically inapparent denervation in asymptomatic limbs, and to rule out a potentially treatable demyelinating or conduction block neuropathy. Patients presenting with the combination of arm muscle denervation coupled with upper motor neuron signs in the legs, require magnetic resonance imagining of the cervical spinal cord to rule out a compressive lesion, most usually spondylitic radiculomyelopathy.

Paraproteinaemia is found in up to 5 per cent of motor neuron diseases, sometimes raising the question of an underlying lymphoid neoplasm. However, most paraproteinaemia-related motor neuron diseases are pure lower motor neuron disorders, often motor neuropathies, rather than amyotrophic lateral sclerosis. An amyotrophic lateral sclerosislike disorder is seen occasionally to accompany underlying lymphoproliferative disorders, treatment of which does not seem to help the neurological disease. Thyrotoxicosis or hyperparathyroidism are reported to simulate motor neuron disease occasionally, but this rarely proves to be an issue in everyday neurological practice. The serum creatine kinase level is often measured because of the question of myopathy, particularly in predominantly proximal and symmetric weakness, but it should be noted that moderate rises in this enzyme level often accompany the denervation of amyotrophic lateral sclerosis. If the question of myopathy persists, muscle biopsy should be undertaken; this can be particularly valuable where the presence of mild bulbar symptoms in patients with proximal weakness raises the question of an inclusion body myositis. Examination of the spinal fluid is rarely helpful in diagnosing motor neuron disease, and slight rises in the protein content occur in a few patients with amyotrophic lateral sclerosis. However, spinal fluid protein levels exceeding 1 g/l, especially if accompanied by lymphocytosis, should raise the question of an underlying tumour.

Inherited forms

Five to 10 per cent of amyotrophic lateral sclerosis is inherited, generally displaying autosomal dominance. There are no particular clinical features, or differences in survival, which distinguish the inherited forms. Usually the clini-

cal phenotype is constant through the generations, but occasional pedigrees show mixtures of amyotrophic lateral sclerosis with spinal muscular atrophy or primary lateral sclerosis. Roughly 20 per cent of familial amyotrophic lateral sclerosis is associated with the 40 different missense mutations of the Cu/Zn superoxide dismutase (SOD1) gene on chromosome 21, which catalyses conversion of toxic superoxide anion radicals to hydrogen peroxide. The disease associated with various SOD1 mutations shows varying degrees of penetrance and a variable phenotype. A slowly progressive form of amyotrophic lateral sclerosis occurs in Tunisia, with onset at 12 years of age (range 3-25 years), autosomal recessive inheritance, and usually with prominent bulbar involvement. It bears similarities to an early onset and relatively benign form seen in India, the so-called Madras form. A similar autosomal dominant form of juvenile onset amyotrophic lateral sclerosis, without significant bulbar or respiratory muscle weakness and only slowly progressive, has been described in a large Maryland family and linked to chromosome 9, whereas the autosomal recessive forms have been linked to chromosome 2 or 15.

Pathology and aetiology

The most striking neuropathological change is loss of large motor neurons from the anterior horns of the cervical and lumbar enlargements of the spinal cord. Similar loss occurs from the hypoglossal and other motor nuclei of the brainstem but the ocular motor nuclei are rarely affected.

Spheroids, composed of interwoven bundles of disorganized neurofilaments, are evident in the proximal axons of motor neurons in the anterior horn in two-thirds of sporadic cases. These spheroids within the proximal axon are a distinctive feature, appearing as an early pathological change in motor neurons. Intracytoplasmic inclusions in motor neurons, known as Bunina bodies, are also characteristic. Loss or shrinkage of giant Betz cells from the precentral gyrus of the cerebral cortex is associated with fibre loss from the pyramidal tracts, particularly obviously in the spinal cord and lower brainstem. At autopsy of advanced cases there is often evidence of a lesser degree of neuronal loss from other areas of the nervous system, including dorsal root ganglia and the dorsal (Clarke's) nuclei of the spinal cord.

The cause of sporadic amyotrophic lateral sclerosis is unknown. There is evidence for various risk factors, but none are invariably associated and it is possible that motor neuron degeneration is a singular expression of diverse aetiological factors. Particular associations with rural populations and with trauma have been noted. Many have searched inconclusively for a viral cause for amyotrophic lateral sclerosis; recent tantalizing evidence, yet to be confirmed, showed enterovirus nucleic acid sequences in anterior horn neurons in 88 per cent of affected spinal cords, compared to only 3 per cent of controls. Given the superoxide dismutase (SOD1) mutation underlying some cases of he-

reditary amyotrophic lateral sclerosis, it will be interesting to discover whether acquired disorders of free-radical detoxication underlie the sporadic form of the disease. A motor neuron degeneration occurs in transgenic mice expressing human mutant SOD1; such models provide the potential for screening new therapies. Transgenic mice overexpressing a neurofilament subunit develop progressive weakness with massive accumulations within motor neurons of neurofilaments resembling spheroids. Synaptosomes derived from affected regions of spinal cord in amyotrophic lateral sclerosis show defective uptake of the potentially toxic excitatory amino-acid neurotransmitter, glutamate. This observation led to the glutamate excitotoxicity hypothesis from which the drug riluzole was developed.

Epidemiology

Amyotrophic lateral sclerosis occurs throughout the world. Traditionally the incidence has been considered to lie between 0.4 and 1.8 per 100000, and the prevalence 4-6 per 100000. More contemporary studies with more confident ascertainment note that many elderly patients are diagnosed often outside neurology departments, and that there is an increasing incidence with age, leading to incidences of 2.25-2.6 per 100 000 in Denmark and Scotland. Case-control studies do not identify any ubiquitous risk factor, although the odds ratios are increased by previous long-bone fractures, manual work, and occupational exposures to lead, solvents, or chemicals. Men are up to twice as commonly affected as women. On the Pacific island of Guam, the incidence of motor neuron disease, often associated with parkinsonism and dementia, has fallen from 87 per 100000 in 1962 to 5 per 100000 in 1985. The reasons for the previous high incidence in Guam are unknown, speculation has centred around the possible role of a dietary excitotoxin found in the locally consumed *Gycas circinalis* flour and upon dietary consumption of calcium and aluminium.

Prognosis and treatment

The severity and extensiveness of muscular weakness progress remorselessly in amyotrophic lateral sclerosis. Death results generally from ventilatory respiratory failure; inhalational pneumonia, or choking and malnutrition may contribute. Bedsores are relatively infrequent despite the immobility of many patients. There is an increased vulnerability to longbone fractures.

Patients with a bulbar onset have the worst prognosis. Their median survival is approximately 20 months from the onset of bulbar symptoms, with only 5 per cent surviving at 5 years. Median survival for those with spinal onset is somewhat better, at 29 months, with nearly 15 per cent surviving at 5 years. It seems that mortality has increased in recent decades and that this cannot be explained solely by the increasing age of the population. Alternative diagnoses,

such as X-linked bulbospinal neuronopathy, should be considered in those patients surviving for an unexpectedly long time. Occasional patients have a subacute and reversible syndrome resembling the spinal form of amyotrophic lateral sclerosis without bulbar involvement, and recover spontaneously within 5-12 months of symptom onset. Such cases are so extraordinarily rare that they should not affect the physician's prognostication.

Trials of drug therapy have concentrated upon slowing the downhill progression of disability or improving survival. The antiglutamate agent riluzole, administered orally, has been licensed for treatment of amyotrophic lateral sclerosis. The 100 mg dosage improved the chance of tracheostomy-free survival at 18 months by an extra 35 per cent, although there was no significant benefit on muscle function. Criticisms of this study have included the nature of the Cox model statistical adjustment, and it should be noted that more of the placebo group had bulbar features at entry to the study. Riluzole is generally well tolerated by patients; nausea, gastrointestinal upset, and raised transaminase enzyme levels may occur, and usually resolve with dosage reduction. Ineffective therapeutic trials have included mixtures of branched-chain amino acids, dextromethorphan, total lymphoid irradiation, and the free-radical scavenger, acetylcysteine.

SPINAL CORD DISORDERS

Cord lesions can lead to motor, sensory, or sphincter disturbances or to some combination of these deficits. Depending upon whether it is unilateral or bilateral, a lesion above C5 may cause either an ipsilateral hemiparesis or quadriparesis. With lesions located lower in the cervical cord, involvement of the upper limbs is partial, and a lesion below T1 affects only the lower limbs on one or both sides. The unilateral involvement of the posterior columns of the cord leads to ipsilateral loss of position and vibration sense. In addition, any disturbance in function of the spinothalamic tracts in the anterolateral columns impairs contralateral pain and temperature appreciation below the level of the lesion.

Spasticity is a common accompaniment of upper motor neuron lesions and may be especially troublesome below the level of the lesion in patients with myelopathies. When the legs are weak, the increased tone of spasticity may help to support the patient in the upright position. Marked spasticity, however, may lead to deformity, interfere with toilet functions, and cause painful flexor or extensor spasms. Pharmacologic management includes treatment with diazepam, baclofen, dantrolene, or tizanidine, but reduction in tone may lead to increased disability from leg weakness.

TRAUMATIC MYELOPATHY

While cord damage may result from whiplash (recoil) injury, severe injury to the cord usually relates to fracture-dislocation in the cervical, lower thoracic, or upper lumbar region.

Clinical Findings

A. Total Cord Transection. Total transection results in immediate permanent paralysis and loss of sensation below the level of the lesion. Although reflex activity is lost for a variable period after the injury, a persistent increase in reflex function follows.

1. In the acute stage, there is flaccid paralysis with loss of tendon and other reflexes, accompanied by sensory loss and by urinary and fecal retention. This is the stage of **spinal shock**.

2. Over the following weeks, as reflex function returns, the clinical picture of a spastic paraplegia or quadriplegia emerges, with brisk tendon reflexes and extensor plantar responses; however, a flaccid, atrophic (lower motor neuron) paralysis may affect muscles innervated by spinal cord segments at the level of

the lesion, where anterior horn cells are damaged. The bladder and bowel now regain some reflex function, so that urine and feces are expelled at intervals.

3. Flexor or extensor spasms of the legs may become increasingly troublesome and are ultimately elicited by even the slightest cutaneous stimulus, especially in the presence of bedsores or a urinary tract infection. Eventually, the patient assumes a posture with the legs in flexion or extension, the former being especially likely with cervical or complete cord lesions.

B. Less Severe Injury. With lesser degrees of injury, the neurologic deficit is less severe and less complete, but patients may be left with a mild paraparesis or quadriparesis or a distal sensory disturbance. Sphincter function may also be impaired urinary urgency and urgency incontinence are especially common. Hyperextension injuries of the neck can lead to focal cord ischemia that causes bibrachial paresis (weakness of both arms) with sparing of the legs and variable sensory signs.

Treatment

A. Immobilization. Initial treatment consists of immobilization until the nature and extent of the injury are determined. If there is cord compression, urgent decompressive surgery will be necessary. An unstable spine may require surgical fixation, and vertebral dislocation may necessitate spinal traction.

B. Corticosteroids. Corticosteroids (eg, methylprednisolone, 30 mg/kg intravenous bolus, followed by intravenous infusion at 5.4 mg/kg/h for 24 hours) can improve motor and sensory function at 6 months when treatment is begun within 8 hours of traumatic spinal cord injury. The mechanism of the action is unknown, but it may involve the inhibition of lipid peroxidation and the improvement of blood flow to the injured spinal cord.

C. Painful Spasms. Painful flexor or extensor spasms can be treated with drugs that enhance spinal inhibitory mechanisms (baclofen, diazepam) or uncouple muscle excitation from contraction (dantrolene). Baclofen should be given 5 mg orally twice daily to 30 mg four times daily; diazepam, 2 mg orally twice daily up to as high as 20 mg three times daily; and dantrolene, 25 mg/d orally to 100 mg four times daily. Tizanidine, a central α_2-agonist, is as effective as these other agents but its precise mechanism of action is unclear. The daily dose is built up gradually, usually to 8 mg three times daily. Side effects include dryness of the mouth, somnolence, and hypotension, but the drug is usually well tolerated. Patients who fail to benefit from or who cannot tolerate sufficient doses of oral medications may respond to intrathecal infusion of baclofen.

All these drugs may increase functional disability by reducing tone. Dantrolene may also increase weakness and should be avoided in patients with severely compromised respiratory function.

D. Skin Care. Particular attention must be given to skin care, avoiding continued pressure on any single area.

E. Bladder and Bowel Disorders. Depending on the severity of the injury, catheterization may be necessary initially. Subsequently, the urgency and frequency of the spastic bladder may respond to a parasympatholytic drug such as oxybutinin, 5 mg three times daily. Suppositories and enemas will help maintain regular bowel movements and may prevent or control fecal incontinence.

CHRONIC ADHESIVE ARACHNOIDITIS

This inflammatory disorder is usually idiopathic but can follow subarachnoid hemorrhage; meningitis; intrathecal administration of penicillin, radiologic contrast materials, and certain forms of spinal anesthetic; trauma; and surgery.

The usual initial complaint is of constant radicular pain, but in other cases there is lower motor neuron weakness because of the involvement of anterior nerve roots. Eventually, a spastic ataxic paraparesis develops, with sphincter involvement. CSF protein is elevated, and the cell count may be increased. Myelography shows a characteristic fragmentation of the contrast material into pockets; MRI may disclose inflammation. Treating this aseptic inflammatory leptomeningeal process with steroids or with nonsteroidal anti-inflammatory analgesics may be helpful. Surgery may be indicated in cases with localized cord involvement.

VASCULAR MYELOPATHIES

Infarction of the Spinal Cord

This rare event generally occurs only in the territory of the anterior spinal artery. This artery, which supplies the anterior two-thirds of the cord, is itself supplied by only a limited number of feeding vessels, while the paired posterior spinal arteries are supplied by numerous feeders at many different levels. Thus, anterior spinal artery syndrome usually results from interrupted flow in one of its feeders. Causes include trauma, dissecting aortic aneurysm, aortography, polyarteritis nodosa, and hypotensive crisis. Since the anterior spinal artery is particularly well supplied in the cervical region, infarcts almost always occur more caudally.

The typical clinical presentation is with the acute onset of a flaccid, areflexic paraparesis that, as spinal shock wears off after a few days or weeks, evolves into a spastic paraparesis with brisk tendon reflexes and extensor plantar responses. In addition, there is dissociated sensory impairment-pain and temperature appreciation are lost, but there is sparing of vibration and position sense because the posterior columns are supplied by the posterior spinal arteries.

Hematomyelia

Hemorrhage into the spinal cord is rare; it is caused by trauma, a vascular anomaly, a bleeding disorder, or anticoagulant therapy. A severe cord syndrome develops acutely and is usually associated with blood in the CSF. The prognosis depends on the extent of the hemorrhage and the rapidity with which it occurs.

Epidural or Subdural Hemorrhage

Spinal epidural or subdural hemorrhage can occur in relation to trauma or tumor and as a complication of anticoagulation, aspirin therapy, thrombocytopenia, coagulopathy, epidural catheters, or lumbar puncture. It occasionally occurs spontaneously. The likelihood of hemorrhage following lumbar puncture – usually epidural in location – is increased when a disorder of coagulation is present. Therefore, the platelet count, prothrombin time, and partial thromboplastin time should be determined before lumbar puncture is performed, and if anticoagulant therapy is to be instituted, it should be delayed for at least 1 hour following the procedure. Patients with less than 20,000 platelets/mm^3 or those with rapidly falling counts (as high as 50,000) should be transfused prior to lumbar puncture. Spinal epidural hemorrhage usually presents with back pain that may radiate in the distribution of one or more spinal nerve roots; it is occasionally painless. Paraparesis or quadriparesis, sensory disturbances in the lower limbs, and bowel and bladder dysfunction may develop rapidly, necessitating urgent CT scan, MRI, or myelography, and surgical evacuation of the hematoma.

Arteriovenous Malformation (AVM)

This may present with subarachnoid hemorrhage or with myelopathy. Most of these lesions involve the lower part of the cord. Symptoms include motor and sensory disturbances in the legs and disorders of sphincter function. Pain in the legs or back is often conspicuous. On examination, there may be an upper, a lower, or a mixed motor deficit in the legs, while sensory deficits are usually extensive but occasionally radicular; the signs indicate an extensive lesion in the longitudinal axis of the cord. In patients with cervical lesions, symptoms and signs may also be present in the arms. A bruit is sometimes audible over the spine, and there may be a cutaneous angioma. The diagnosis is suggested by the MRI appearance and the myelographic finding of serpiginous filling defects caused by enlarged vessels, and it is confirmed by selective spinal arteriography. Spinal MRI is sometimes normal despite the presence of an AVM and therefore cannot be relied upon to exclude this diagnosis.

Most lesions are extramedullary and posterior to the cord; they can be treated by embolization or by ligation of feeding vessels and excision of the anomalous arteriovenous nidus of the malformation, which is usually dural in location. Left untreated, the patient is likely to become increasingly disabled until chair or bed-bound.

CERVICAL SPONDYLOSIS

Cervical spondylosis is characterized by any or all of the following: pain and stiffness in the neck; pain in the arms, with or without a segmental motor or sensory deficit in the arms; and an upper motor neuron deficit in the legs. It results from chronic cervical disk degeneration, with herniation of disk material, secondary calcification, and associated osteophytic outgrowths. It can lead to involvement of one or more nerve roots on either or both sides and to myelopathy related to compression, vascular insufficiency, or recurrent minor trauma to the cord.

Patients often present with neck pain and limitation of head movement or with occipital headache. In some cases, radicular pain and other sensory disturbances occur in the arms, and there may be weakness of the arms or legs. Examination commonly reveals restricted lateral flexion and rotation of the neck. There may be a segmental pattern of weakness or dermatomal sensory loss in one or both arms, along with depression of those tendon reflexes mediated by the affected root(s). Cervical spondylosis tends to affect particularly the C5 and C6 nerve roots, so there is commonly weakness of muscles (eg, deltoid, supra- and infraspinatus, biceps, brachioradialis) supplied from these segments, pain or sensory loss about the shoulder and outer border of the arm and forearm, and depressed biceps and brachioradialis reflexes. If there is an associated myelopathy, upper motor neuron weakness develops in one or both legs, with concomitant changes in tone and reflexes. There may also be posterior column or spinothalamic sensory deficits.

Plain x-rays show osteophyte formation, narrowing of disk spaces, and encroachment on the intervertebral foramina. MRI, CT scanning, or even myelography may be necessary to confirm the diagnosis and exclude other structural causes of myelopathy. The CSF obtained at the time of myelography is usually normal, but the protein concentration may be increased, especially if there is a block in the subarachnoid space. Electrophysiologic studies, especially needle electromyography, are helpful in identifying a radiculopathy and in determining whether degenerative anatomic abnormalities of the cervical spine are of any clinical relevance.

Spondylotic myelopathy may resemble myelopathy caused by such disorders as multiple sclerosis, motor neuron disease, subacute combined degeneration, cord tumor, syringomyelia, or hereditary spastic paraplegia. Moreover, degenerative changes in the spine are common in the middle-aged and elderly and may coincide with one of these other disorders.

Treatment with a cervical collar to restrict neck movements may relieve any pain. Operative treatment may be necessary to prevent further progression if there is a significant neurologic deficit; it may also be required if the root pain is severe, persistent, and unresponsive to conservative measures.

CONGENITAL ANOMALIES

A combination of corticospinal and cerebellar signs may be found in the limbs of patients with congenital skeletal abnormalities such as platybasia (flattening of the base of the skull) or basilar invagination (an upward bulging of the margins of the foramen magnum). Syringomyelia (cavitation of the cord), which can be congenital or acquired, may lead to a lower motor neuron deficit, a dissociated sensory loss in the arms, and upper motor neuron signs in the legs. Because the sensory findings are so characteristic, this disorder, which is frequently associated with Arnold-Chiari malformation.

SYRINGOMYELIA

Syringomyelia is cavitation of the spinal cord. Communicating syringomyelia – with communication between the central canal of the cord and the cavity – is a hydrodynamic disorder of the CSF pathways. In noncommunicating syringomyelia, there is cystic dilation of the cord, which is not in communication with the CSF pathways. The precise clinical disturbance that results depends upon the site of cavitation. Typically, there is a **dissociated sensory loss** at the level of the lesion; pinprick and temperature appreciation are impaired, but light touch sensation is preserved. The sensory loss may be reflected by the presence of painless skin ulcers, scars, edema, hyperhidrosis, neuropathic joints, resorption of the terminal phalanges, and other disturbances. Weakness and wasting of muscles occur at the level of the lesion because of the involvement of the anterior horns of the cord. A pyramidal deficit and sphincter disturbances sometimes occur below the level of the lesion because of gliosis or compression of the corticospinal pathways in the lateral columns of the cord. The tendon reflexes may be depressed at the level of the lesion – because of interruption of their afferent, central, or efferent pathways – and increased below it. Scoliosis is a common accompaniment of cord cavitation. Cavitation commonly occurs in the cervical region; this can cause a cape-like distribution of sensory loss over one or both shoulders, diffuse pain in the neck, and radicular pain in the arms; involvement of the T1 segment frequently leads to ipsilateral Horner's syndrome. If the cavitation involves the lower brainstem (syringobulbia), there may also be ipsilateral tongue wasting, palatal weakness, vocal cord paralysis, dissociated trigeminal sensory loss, and other evidence of brainstem involvement.

Communicating syringomyelia is often associated with developmental anomalies of the brainstem and foramen magnum region (Arnold-Chiari malformation) or with chronic arachnoiditis of the basal cisterns. Arnold-Chiari malformation can lead to hydrocephalus, cerebellar ataxia, pyramidal and sensory deficits in the limbs, and abnormalities of the lower cranial nerves, alone or

in any combination. Myelography, MRI, or CT scanning of the foramen magnum region confirms the diagnosis. Treatment is surgical.

Noncommunicating syringomyelia is often due to trauma, intramedullary tumors, or spinal arachnoiditis. Posttraumatic syringomyelia generally occurs in patients with preexisting, severe neurologic deficits from spinal trauma after an interval of several years, although rarely it may develop only a few months after the original injury. Presentation is with increase in a previously stable deficit; weakness, impaired sensation, and spasticity are often conspicuous, and radicular pain may be distressing.

Treatment depends upon the underlying cause. Decompression of a distended syrinx may provide transient benefit. In the case of communicating syringomyelia associated with Arnold-Chiari malformation, removal of the posterior rim of the foramen magnum and amputation of the cerebellar tonsils are sometimes helpful. The cord cavity should be drained, and, if necessary, an outlet should be made for the fourth ventricle. Posttraumatic syringomyelia is treated by surgery if it is causing a progressive neurologic deficit or intolerable pain. A variety of surgical approaches have been used, including various draining procedures from the cord cavity, myelotomy, and formation of surgical meningocele. Radicular pain and sensory disturbances are usually helped, whereas spasticity responds less satisfactorily.

SUBACUTE COMBINED DEGENERATION (VITAMIN B_{12} DEFICIENCY)

Vitamin B_{12} deficiency may result from impaired absorption by the gastrointestinal tract such as occurs in pernicious anemia or because of gastrointestinal surgery, sprue, or infection with fish tapeworm; it can also be caused by a strictly vegetarian diet. It may affect the spinal cord, giving rise to the syndrome of subacute combined degeneration. Onset is with distal paresthesias and weakness in the extremities (involvement of the hands occurs relatively early), followed by the development of spastic paraparesis, with ataxia from the impairment of postural sensation in the legs. Lhermitte's sign may be present, and examination reveals a combined posterior column (vibration and joint position sense) and pyramidal deficit in the legs. Plantar responses are extensor, but tendon reflexes may be increased or depressed, depending on the site and severity of the involvement. Signs of cord involvement can be accompanied by centrocecal scotoma or optic atrophy from optic (II) nerve involvement, by behavioral or psychiatric changes, or by peripheral neuropathy. The neurologic manifestations are often accompanied by macrocytic megaloblastic anemia, but this is not invariably present.

The serum vitamin B_{12} level is low in untreated cases. If malabsorption of vitamin B_{12} is the cause, the Schilling test is abnormal, and there is usually gastric achlorhydria with pernicious anemia. Hematologic findings may be normal, however, especially if folic acid supplements have been given.

Treatment is with vitamin B_{12} given by intramuscular injection daily (50-1000 μg) for 2 weeks, then weekly (100 μg) for 2 months, and monthly (100 μg) thereafter. Note that folic acid supplements do not help the neurologic disorder; in addition, they may mask associated anemia.

TABES DORSALIS

This type of neurosyphilis, now rare, is characterized mainly by sensory symptoms and signs that indicate marked involvement of the posterior roots, especially in the lumbosacral region, with resulting degeneration in the posterior columns of the spinal cord. Common complaints are of unsteadiness, sudden lancinating somatic pains, and urinary incontinence. Visceral crises characterized by excruciating abdominal pain also occur. Examination reveals marked impairment of vibration and joint position sense in the legs, together with an ataxic gait and Romberg's sign. Deep pain sensation is impaired, but superficial sensation is generally preserved. The bladder is often palpably enlarged; because it is flaccid and insensitive, there is overflow incontinence. Tendon reflexes are lost, and the limbs are hypotonic. Sensory loss and hypotonicity may lead to the occurrence of hypertrophic (Charcot) joints. In many patients there are other signs of neurosyphilis, including Argyll Robertson pupils, optic atrophy, ptosis, a variable ophthalmoplegia, and, in some cases, pyramidal and mental changes from cerebral involvement (taboparesis). Treatment is of the underlying infection.

TUMORS & CORD COMPRESSION

Common causes of cord compression are disk protrusion, trauma, and tumors; in certain parts of the world, tuberculous disease of the spine is also a frequent cause. Rare but important causes include epidural abscess and hematoma.

Classification

Tumors can be divided into two groups: intramedullary (10%) and extramedullary (90%). Ependymomas are the most common type of intramedullary tumor, and the various types of gliomas make up the remainder. Extramedullary tumors can be either extradural or intradural in location. Among the primary ex-

tramedullary tumors, neurofibromas and meningiomas are relatively common and are benign; they can be intra- or extradural. Carcinomatous metastases (especially from bronchus, breast, or prostate), lymphomatous or leukemic deposits, and myeloma are usually extradural.

Clinical Findings

Irrespective of its nature, a tumor can lead to cord dysfunction and a neurologic deficit by direct compression, ischemia secondary to arterial or venous obstruction, or, in the case of intramedullary lesions, by invasive infiltration.

A. Symptoms. Symptoms may develop insidiously and progress gradually or – as is often the case with spinal cord compression from metastatic carcinoma – exhibit a rapid course.

Pain is a conspicuous feature – and usually the initial abnormality – in many patients with extradural lesions; it can be radicular, localized to the back, or experienced diffusely in an extremity and is characteristically aggravated by coughing or straining.

Motor symptoms (heaviness, weakness, stiffness, or focal wasting of one or more limbs) may develop, or there may be paresthesias or numbness, especially in the legs. When sphincter disturbances occur, they usually are particularly disabling.

B. Signs. Examination sometimes reveals localized spinal tenderness. Involvement of anterior roots leads to an appropriate lower motor neuron deficit, and involvement of posterior roots leads to dermatomal sensory changes at the level of the lesion. Involvement of pathways traversing the cord may cause an upper motor neuron deficit below the level of the lesion and a sensory deficit with an upper level on the trunk. The distribution of signs varies with the level of the lesion and may take the form of Brown-Sequard or central cord syndrome.

Investigative Studies

The CSF is often xanthochromic, with a greatly increased protein concentration, a normal or elevated white blood cell count, and normal or depressed glucose concentration; Queckenstedt's test at lumbar puncture may reveal a partial or complete block. A plain x-ray of the spine mayor may not be abnormal, and myelography, CT scanning, or MRI is necessary to delineate the lesion and localize it accurately.

Treatment

Treatment depends upon the nature of the lesion. Extradural metastases must be treated urgently. Depending upon the nature of the primary neoplasm, they are best managed by analgesics, corticosteroids, radiotherapy, and hormonal treatment; decompressive laminectomy is often unnecessary. Intradural (but extramedullary) lesions are best removed if possible. Intramedullary tumors are

treated by decompression and surgical excision when feasible and by radiotherapy.

Prognosis

The prognosis depends upon the cause and severity of the cord compression before it is relieved. Cord compression by extradural metastasis is usually manifested first by pain alone and may progress rapidly to cause permanent impairment of motor, sensory, and sphincter function. Therefore, the diagnosis must be suspected early in any patient with cancer and spinal or radicular pain, who must be investigated immediately. Reliance on motor, sensory, or sphincter disturbances to make the diagnosis will unnecessarily delay treatment and worsen the outcome.

ANTERIOR HORN CELL DISORDERS

Disorders that predominantly affect the anterior horn cells are characterized clinically by wasting and weakness of the affected muscles without accompanying sensory changes. Electromyography shows changes that are characteristic of chronic partial denervation, with abnormal spontaneous activity in resting muscle and a reduction in the number of motor units under voluntary control; signs of reinnervation may also be present. Motor conduction velocity is usually normal but may be slightly reduced, and sensory conduction studies are normal. Muscle biopsy shows the histologic changes of denervation. Serum CPK may be slightly elevated, but it never reaches the extremely high values seen in some muscular dystrophies. The clinical features and outlook depend in part on the patient's age at onset. The cause of these disorders is unknown, but the genetic basis for some of them is being clarified. The infantile and intermediate spinal muscular atrophies are now recognized to represent allelic mutations of a gene localized to the long arm of chromosome 5.

Infantile Spinal Muscular Atrophy (Werdnig-Hoffmann Disease)

This autosomal recessive disorder usually manifests itself within the first 3 months of life. The infant is floppy and may have difficulty with sucking, swallowing, or ventilation. In established cases, examination reveals impaired swallowing or sucking, atrophy and fasciculation of the tongue, and muscle wasting in the limbs that is sometimes obscured by subcutaneous fat. The tendon reflexes are normal or depressed, and the plantar responses may be absent. There is no sensory deficit. The disorder is rapidly progressive, generally leading to death from respiratory complications by about age 3 years. The cause is unknown, and there is no effective treatment.

Intermediate Spinal Muscular Atrophy (Chronic Werdnig-Hoffmann Disease)

This also has an autosomal recessive mode of inheritance but usually begins in the latter half of the first year of life. Its main clinical features are wasting and weakness of the extremities; bulbar weakness occurs less commonly. The disorder progresses slowly, ultimately leading to severe disability with kyphoscoliosis and contractures, but its course is more benign than the infantile variety described above, and many patients survive into adulthood. Treatment is essentially supportive and directed particularly at the prevention of scoliosis and other deformities.

Juvenile Spinal Muscular Atrophy (Kugelberg-Welander Disease)

Generally this disorder develops in childhood or early adolescence, on either a hereditary or sporadic basis. The usual mode of inheritance is autosomal recessive, but cases with autosomal dominant or X-linked recessive inheritance also occur. It particularly tends to affect the proximal limb muscles, while there is generally little involvement of the bulbar musculature. It follows a gradually progressive course, leading to disability in early adult life. The proximal weakness may lead to a mistaken diagnosis of muscular dystrophy, but serum CPK determination, electromyography, and muscle biopsy will differentiate the disorders. There is no effective treatment.

MOVEMENT DISORDERS

ESSENTIAL TREMOR

A postural tremor may be prominent in otherwise normal subjects. Although the pathophysiologic basis of this disorder is uncertain, it often has a familial basis with an autosomal dominant mode of inheritance. Two responsible genes have been identified.

Symptoms may develop in the teenage or early adult years but often do not appear until later. The tremor usually involves one or both hands or the head and voice, while the legs tend to be spared. Examination usually reveals no other movement disorders or some other abnormalities. Although the tremor may become more conspicuous with time, it generally leads to little disability other than cosmetic and social embarrassment. In occasional cases, tremor interferes with the ability to perform fine or delicate tasks with the hands; handwriting is sometimes severely impaired. Speech is affected when the laryngeal muscles are involved. Patients commonly report that a small quantity of alcohol provides remarkable but transient relief; the mechanism is not known.

If treatment is warranted, propranolol, 40-120 mg orally twice daily, can be prescribed-but it will need to be taken for an indefinite period. Alternatively, if tremor is particularly disabling under certain predictable circumstances, it can be treated with a single oral dose of 40-120 mg of propranolol taken in anticipation of the precipitating circumstances. Primidone has also been effective, but patients with essential tremor are often very sensitive to this drug, so that it must be introduced more gradually than when it is used to treat epilepsy. Patients are therefore started on 50 mg/d and the daily dose increased by 50 mg every 2 weeks until benefit occurs or side effects limit further increments. A dose of 100 or 150 mg three times a day is often effective. Occasional patients respond to alprazolam, up to 3 mg/d in divided doses.

Some patients have disabling tremor that is unresponsive to pharmacologic measures. Thalamotomy may be helpful, but a significant morbidity is associated with bilateral procedures. High-frequency thalamic stimulation by an implanted electrode is an effective alternative to thalamotomy and has a low morbidity. It may be particularly useful for treatment of the unoperated side in patients who have already undergone unilateral thalamotomy.

PARKINSONISM

Parkinsonism occurs in all ethnic groups; in the United States and western Europe it has a prevalence of 1-2/1000 population, with an approximately equal

sex distribution. The disorder becomes increasingly common with advancing age. It is characterized by tremor, hypokinesia, rigidity, and abnormal gait and posture. Etiology of parkinsonism may be different.

A. Idiopathic. A very common variety of parkinsonism occurs without obvious cause; this idiopathic form is called Parkinson's disease or paralysis agitans.

B. Encephalitis Lethargica. In the first half of the twentieth century, parkinsonism often developed in patients with a history of von Economo's encephalitis. Since this type of infection is not now encountered, cases of postencephalitic parkinsonism are becoming increasingly rare.

C. Drug- or Toxin-Induced Parkinsonism.

1. Therapeutic drugs-Many drugs, such as phenothiazines, butyrophenones, metoclopramide, reserpine, and tetrabenazine, can cause a reversible parkinsonian syndrome.

2. Toxic substances. Toxins such as manganese dust or carbon disulfide can also lead to parkinsonism, and the disorder may appear as a sequela of severe carbon monoxide poisoning.

3. MPTP (1-Methyl-4-phenyl-1,2,5,6-tetrahydropyridine). A drug-induced form of parkinsonism has been described in individuals who synthesized and self-administered a meperidine analogue, MPTP. This compound is metabolized to a toxin that selectively destroys dopaminergic neurons in the substantia nigra and adrenergic neurons in the locus ceruleus and induces a severe form of parkinsonism in humans and in subhuman primates. The ability of this drug to reproduce neurochemical, pathologic, and clinical features of Parkinson's disease suggests that an environmental toxin could be responsible for the idiopathic disorder. MPTP-induced parkinsonism may provide a model that could assist in development of new drugs for treatment of this disease.

D. Parkinsonism Associated with Other Neurologic Diseases. Parkinsonism that occurs in association with symptoms and signs of other neurologic disorders is considered briefly below.

E. Familial Parkinsonism. Rarely, parkinsonism occurs on a familial basis. The responsible (alpha-synuclein) gene has recently been identified on the long arm of chromosome 4 in one large kindred in which the disorder was inherited in an autosomal dominant manner.

Pathology. In idiopathic parkinsonism, pathologic examination shows loss of pigmentation and cells in the substantia nigra and other brainstem centers, cell loss in the globus pallidus and putamen, and the presence of eosinophilic intraneural inclusion granules (Lewy bodies) in the basal ganglia, brain stem, spinal cord, and sympathetic ganglia. These inclusion bodies are not seen in postencephalitic parkinsonism; instead there may be nonspecific neurofibrillary degeneration in a number of diencephalic structures as well as changes in the substantia nigra.

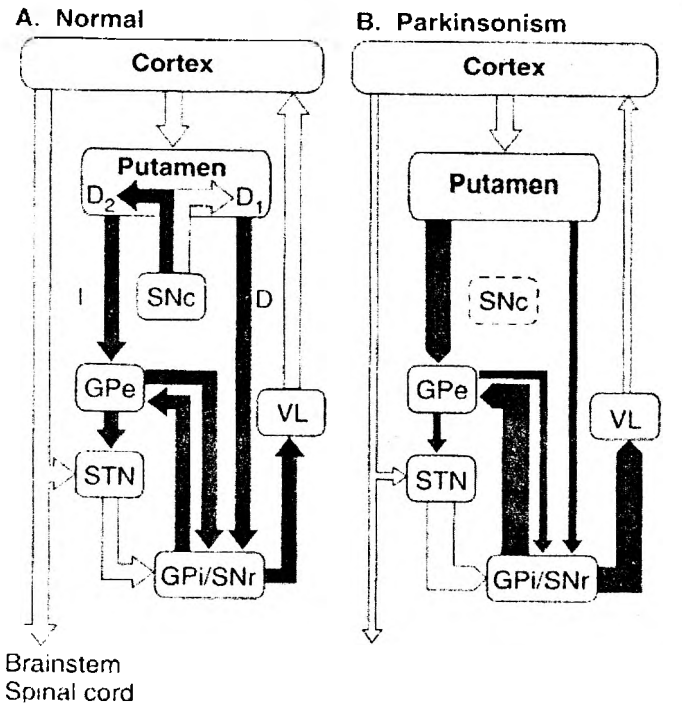


Fig. 18. A model of the basal ganglia and its connections under normal conditions (A) and in the setting of parkinsonism (B). I refers to the indirect pathway and D refers to the direct pathway. Blue arrows indicate inhibitory connections; white arrows indicate excitatory connections. The thickness of the arrows indicates the amount of activity in the various projections. GPe, external segment of globus pallidus; GPi, internal segment of globus pallidus; SNr, substantia nigra pars reticulata; SNc, substantia nigra pars compacta; STN, subthalamic nucleus; VL, ventrolateral thalamus. (From Wichmann T, Vitej J, Delong M, 1995)

Pathogenesis. Both dopamine and acetylcholine are present in the corpus striatum, where they act as neurotransmitters. In idiopathic parkinsonism, it is generally believed that the normal balance between these two antagonistic neurotransmitters is disturbed because of dopamine depletion in the dopaminergic nigrostriatal system. Other neurotrans mitters, such as norepinephrine, are also depleted in the brains of patients with parkinsonism, but the clinical relevance of this deficiency is less clear.

Disorder of the balance of inhibition and excitation within the basal ganglia and its connections via direct and indirect pathways has been proposed to explain the impaired motor function in Parkinson's disease.

Clinical Findings

A. Tremor. The 4- to 6-Hz tremor of parkinsonism is characteristically most conspicuous at rest; it increases at times of emotional stress and often improves during voluntary activity. It commonly begins in the hand or foot, where it takes the fonn of rhythmic flexion-extension of the fingers or of the hand or foot---or of rhythmic pronation-supination of the foreann. It frequently involves the face in the area of the mouth as well. Although it may ultimately be present in all of the limbs, it is not uncommon for the tremor to be confined to one limb--or to the two limbs on one side-for months or years before it becomes more generalized. In some patients tremor never becomes prominent.

B. Rigidity. Rigidity, or increased tone – ie, increased resistance to passive movement – is a characteristic clinical feature of parkinsonism. The disturbance in tone is responsible for the flexed posture of many patients with parkinsonism. The resistance is typically unifonn throughout the range of movement at a particular joint and affects agonist and antagonist muscles alike – in contrast to the findings in spasticity, where the increase in tone is often greatest at the beginning of the passive movement (claspknife phenomenon) and more marked in some muscles than in others. In some instances, the rigidity in parkinsonism is described as cogwheel rigidity because of ratchetlike interruptions of passive movement that may be due, in part, to the presence of tremor.

C. Hypokinesia. The most disabling feature of this disorder is hypokinesia (sometimes called bradykinesia or akinesia)-a slowness of voluntary movement and a reduction in automatic movement, such as swinging the arms while walking. The patient's face is relatively immobile (masklike fades), with widened palpebral fissures, infrequent blinking, a certain fixity of facial expression, and a smile that develops and fades slowly. The voice is of low volume (hypophonia) and tends to be poorly modulated. Fine or rapidly alternating movements are impaired, but power is not diminished if time is allowed for it to develop. The handwriting is small, tremulous, and hard to read.

D. Abnormal Gait and Posture. The patient generally finds it difficult to get up from bed or an easy chair and tends to adopt a flexed posture on standing (Figure 8-6). It is often difficult to start walking: so that the patient may lean farther and farther forward while walking in place before being able to advance. The gait itself is characterized by small, shuffling steps and absence of the arm swing that normally accompanies locomotion; there is generally some unsteadiness on turning, and there may be difficulty in stopping. In advanced cases, the patient tends to walk with increasing speed to prevent a fall (festinating gait) because of the altered center of gravity that results from the abnormal posture.

E. Other Clinical Features. There is often mild blepharoclonus (fluttering of the closed eyelids) and occasionally blepharospasm (involuntary closure of the eyelids). The patient may drool, perhaps because of impairment of swallowing. There is typically no alteration in the tendon reflexes, and the plantar responses are flexor. Repetitive tapping (about twice per second) over the bridge of the nose produces a sustained blink response (Myerson's sign); the response is not sustained in normal subjects. Cognitive decline sometimes occurs but is usually mild and late. Depression and visual hallucinations are frequent.

Differential Diagnosis

The diagnosis may be difficult to make in mild cases. Depression may be accompanied by a somewhat expressionless face, poorly modulated voice, and reduction in voluntary activity; it can thus simulate parkinsonism. Moreover, the two diseases often coexist in the same patient. A trial of antidepressant drug treatment may be helpful if diagnostic uncertainty cannot be resolved by the presence of more widespread neurologic signs indicative of parkinsonism.

Essential (benign, familial) tremor has been considered separately (see earlier). An early age at onset, a family history of tremor, a beneficial effect of alcohol on the tremor, and a lack of other neurologic signs distinguish this disorder from parkinsonism. Furthermore, essential tremor commonly affects the head (causing a nod or head shake); parkinsonism typically affects the face and lips rather than the head.

Diffuse Lewy body disease is a disorder of recently evolving definition. It is marked clinically by the combination of a rapidly progressing neurobehavioral syndrome of dementia and hallucinations and extrapyramidal motor features characteristic of Parkinson's disease. Myoclonus may also be seen. There is only an incomplete response to levodopa, but patients are extremely sensitive to parkinsonian complications of neuroleptics as well as to the side effects of anti parkinsonian drugs.

Wilson's disease can also lead to a parkinsonian syndrome, but other varieties of abnormal movements are usually present as well. Moreover, the early age at onset and the presence of Kayser-Fleischer rings should distinguish Wil-

son's disease from Parkinson's disease, as should the abnormalities in serum and urinary copper and serum ceruloplasmin that occur in Wilson's disease.

Huntington's disease may occasionally be mistaken for parkinsonism when it presents with rigidity and akinesia, but a family history of Huntington's disease or an accompanying dementia, if present, should suggest the correct diagnosis, which can be confirmed by genetic studies.

Shy-Drager syndrome is a degenerative disorder characterized by parkinsonian features, autonomic insufficiency (leading to postural hypotension, anhidrosis, disturbance of sphincter control, impotence, etc), and signs of more widespread neurologic involvement (pyramidal or lower motor neuron signs and often a cerebellar deficit). There is no treatment for the motor deficit, but the postural hypotension may respond to a liberal salt diet; fludrocortisone, 0.1-1 mg/d; midodrine (an a-agonist) 10 mg three times daily; wearing waist-high elastic hosiery; and sleeping with the head up at night.

Striatonigral degeneration is a rare disorder that is associated with neuronal loss in the putamen, globus pallidus, and caudate nucleus, and presents with bradykinesia and rigidity. Antiparkinsonian drugs are typically ineffective. Striatonigral degeneration may be associated with olivopontocerebellar degeneration, in which case the term multiple system atrophy or Shy-Drager syndrome is applied.

Progressive supranuclear palsy is a disorder in which there may be bradykinesia and rigidity, but its characteristic features are loss of voluntary control of eye movements (especially vertical gaze), dementia, pseudobulbar palsy, dysarthria, and axial dystonia. The disorder responds poorly, if at all, to antiparkinsonian drugs.

Cortical basal ganglionic degeneration is characterized clinically by both cortical and basal ganglionic dysfunction. Rigidity, bradykinesia, tremor, postural disturbances, and dystonia are accompanied by such additional deficits as cortical sensory loss, apraxia, focal reflex myoclonus, dementia, or aphasia. Symptoms are often strikingly asymmetric. Treatment with antiparkinsonian medication is usually unrewarding, although some patients do respond to Sinemet.

Creutzfeldt-Jakob disease may be accompanied by parkinsonian features, but dementia is usually present, myoclonic jerking is common, and ataxia is sometimes prominent; there may be pyramidal signs and visual disturbances, and the EEG findings of periodic discharges are usually characteristic.

Normal-pressure hydrocephalus leads to a gait disturbance (often mistakenly attributed to parkinsonism), urinary incontinence, and dementia. CT scanning reveals dilation of the ventricular system of the brain without cortical atrophy. The disorder may follow head injury, intracranial hemorrhage, or meningoencephalitis, but the cause is often obscure. Surgical shunting procedures to bypass any obstruction to the flow of CSF are often beneficial.

Treatment

Early parkinsonism requires no drug treatment, but it is important to discuss with the patient the nature of the disorder and the availability of medical treatment if symptoms become more severe and to encourage activity. Treatment, when indicated, is directed toward restoring the dopaminergic: cholinergic balance in the striatum by blocking the effect of acetylcholine with anticholinergic drugs or by enhancing dopaminergic transmission.

Drugs used in the treatment of Parkinson's disease

Anticholinergics
- Benztropine (Cogentin)
- Trihexyphenidyl (Artane)

Amantadine (Symmetrel)

Levodopa (Sinemet)

Dopamine agonists
- Ergolides
  - Bromocriptine (Parlodel)
  - Pergolide (Permax)
- Nonergolides
  - Pramipexole (Mirapex)
  - Ropinirole (Requip)

MAO-B inhibitor
- Selegiline (Eldepryl)

COMT inhibitor
- Tolcapone (Tasmar)

A. Anticholinergic Drugs. Muscarinic anticholinergic drugs are more helpful in alleviating tremor and rigidity than hypokinesia but are generally less effective than dopaminergic drugs (see below). A number of preparations are available, and individual patients tend to favor different drugs. Among the most commonly prescribed drugs are trihexyphenidyl and benztropine. Common side effects include dryness of the mouth, constipation, urinary retention, and defective pupillary accommodation; these are caused by muscarinic receptor blockade in parasympathetic end organs. Confusion, especially in the elderly, is due to antimuscarinic effects in the brain. Treatment is started with a small dose of one of the anticholinergics; the dosage is then gradually increased until benefit occurs or side effects limit further increments. If treatment is not helpful, the drug is withdrawn and another anticholinergic preparation is tried.

B. Amantadine. Amantadine can be given for mild parkinsonism either alone or in combination with an anticholinergic agent. Its precise mode of action

is unclear. Its advantages are that it improves all the clinical features of parkinsonism, its side effects (restlessness, confusion, skin rashes, edema, disturbances of cardiac rhythm) are relatively uncommon, its effects are exerted rapidly, and it is given in a standard dose of 100 mg orally twice daily. Unfortunately, however, many patients fail to respond to this drug, or its benefit is short-lived.

C. Levodopa. Levodopa, which is converted in the body to dopamine (Figure 8-8), ameliorates all the major clinical features of parkinsonism and, unlike the anticholinergic drugs, is often particularly helpful against hypokinesia. There is controversy about the best time to introduce dopaminergic therapy. Concerns that levodopa loses its effectiveness with time in some patients are probably misplaced, but response fluctuations sometimes occur after it has been used for several years, and these may be particularly disabling and difficult to manage. It may be wise to defer its introduction as long as possible and then use dopamine agonists (discussed below) in conjunction with it to keep the levodopa dose as low as possible.

The most common side effects of levodopa are nausea, vomiting, hypotension, abnormal movements (dyskinesias), restlessness, and confusion. Cardiac arrhythmias occur occasionally. The late dyskinesias and behavioral side effects occur as dose-related phenomena, but reduction in dose may diminish any therapeutic benefit. Treatment with clozapine, a dibenzodiazepine derivative that does not block the therapeutic effects of dopaminergic medication, may relieve confusion and psychotic mental disturbances and, in some instances, the dyskinesias. Clozapine requires regular monitoring of the leukocyte count. Olanzepine and risperidol are alternative agents that may be less effective but do not affect the blood count. Another late complication of levodopa therapy is response fluctuation such as the wearing-off effect, in which deterioration occurs shortly before the next dose is to be taken, or the on-off phenomenon, in which abrupt but transient fluctuations in the severity of parkinsonism occur at frequent intervals during the day, apparently without any relationship to the last dose of levodopa. This sometimes disabling problem is unaffected by concomitant administration of carbidopa. It can be controlled only partly by varying the dosing intervals, administering levodopa 1 hour before meals, restricting dietary protein intake, or providing treatment with dopamine agonists.

Carbidopa is a drug that inhibits dopa decarboxylase, the enzyme responsible for the breakdown of levodopa to its active metabolite, dopamine, but does not cross the blood-brain barrier. Accordingly, if levodopa is given in combination with carbidopa, the breakdown of levodopa is limited outside the central nervous system. The daily dose of levodopa required for benefit and the incidence of nausea, vomiting, hypotension, and cardiac irregularities can be reduced if levodopa is taken in combination with carbidopa. Carbidopa is generally combined with levodopa in a fixed proportion (1: 10 or 1:4) as Sinemet. Treatment is started with a small dose, such as Sinemet 10/100 (mg) or Sinemet 251100 (mg) orally three times daily, and the dose is gradually increased, de-

pending on the response. Most patients ultimately require Sinemet 25/250 (mg) three or four times daily. Carbidopa should total at least 75 mg/d.

Levodopa therapy (either alone or in conjunction with carbidopa) is contraindicated in patients with narrow-angle glaucoma or psychotic illness and should be avoided in patients receiving monoamine oxidase A inhibitors. It should also be used with care in patients with active peptic ulcers or suspected malignant melanomas.

A controlled-release (CR) formulation of Sinemet may reduce response fluctuations and the dosing frequency.

D. Dopamine Agonists. The older agonists are ergot derivatives. Bromocriptine stimulates dopamine Dz receptors. It is perhaps slightly less effective than levodopa in relieving the symptoms of parkinsonism but is less likely to cause dyskinesias or the on-off phenomenon. In consequence, it has been recommended that when dopaminergic therapy is to be introduced, the patient be started on Sinemet, 25/100 three times daily, with bromocriptine then added and gradually increased. The starting dose of bromocriptine is 1.25 mg/d for I week and 2.5 mg/d for the next week, after which the daily dose is increased by 2.5-mg increments every 2 weeks, depending on the response and the development of side effects. Maintenance doses are usually between 2.5 and 10 mg orally three times daily. Side effects are similar to those associated with levodopa therapy, but psychiatric effects such as delusions or hallucinations are especially common, and bromocriptine is therefore contraindicated in patients with a history of psychotic disorders. Relative contraindications to its use are recent myocardial infarction, severe peripheral vascular disease, and active peptic ulceration.

Pergolide also is an ergot derivative and dopamine receptor agonist; unlike bromocriptine, it activates both D_1 and D_2 receptors. Its indications, side effects, and contraindications are similar to those described above for bromocriptine, and it is unclear whether either compound is clinically superior to the other. The starting dose is 0.05 mg orally daily for 2 days, increased by 0.1-0.15 mg/d every 3 days for 12 days and by 0.25 mg/d every 3 days thereafter. The average maintenance dose is 1 mg orally three times daily.

The new dopamine agonists, pramipexole and ropinirole, are not ergot derivatives. They seem more effective than the older agonists and may be used in early or advanced Parkinson's disease. Pramipexole is started at 0.125 mg three times daily; the daily dose is doubled after one week and again after another week; it is then increased by 0.75 mg each week according to response and tolerance. A common maintenance dose is between 0.5 and 1.5 mg three times daily. Ropinirole is started at 0.25 mg three times daily and the total daily dose increased at weekly intervals by 0.75 mg until the fourth week and by 1.5 mg thereafter. Most patients need between 2 and 8 mg three times daily for benefit. Adverse effects of these medications include fatigue, somnolence, nausea, pe-

ripheral edema, dyskinesias, confusion, hallucinations, and orthostatic hypotension.

E. Tolcapone. Tolcapone, recently approved by the FDA, is a catechol-O-methyltransferase inhibitor. Such inhibitors may be used to reduce the dose requirements of and any response fluctuations to Sinemet. Its use leads to more sustained plasma levels of levodopa, with improved transport into the blood and across the blood-brain barrier. Side effects include diarrhea, confusion, dyskinesias, and abnormalities of liver function tests. Most patients require a dose of 100 mg three times daily.

F. Selegiline. Selegiline (also called eldepryl or deprenyl) is a monoamine oxidase type B inhibitor and therefore inhibits the metabolic breakdown of dopamine. It thus enhances the antiparkinsonian effect of levodopa and may reduce mild on-off fluctuations in responsiveness. Some clinical studies suggest that selegiline may also delay the progression of Parkinson's disease, although the evidence is incomplete in this regard; when used for neuroprotection, selegiline is best kept for patients with mild disease. The dose is 5 mg orally twice daily, usually given early in the day to avoid insomnia.

G. Surgery. Surgical treatment of parkinsonism by thalamotomy or pallidotomy is often helpful when patients become unresponsive to pharmacologic measures or develop intolerable adverse reactions to antiparkinsonian medication. Lesions of the internal segment of the globus pallidus (GPi), for example, will attenuate its unbalanced inhibitory output. Treatment by surgery is sometimes helpful in relatively young patients with predominantly unilateral tremor and rigidity that have failed to respond to medication; thalamotomy is more helpful for tremor and pallidotomy for hypokinesia. Diffuse vascular disease or dementia is a contraindication to this approach. The rate of significant complications is less than 5% after unilateral pallidotomy or thalamotomy, but about 20% or more after bilateral procedures, which are therefore best avoided.

Autologous or fetal adrenal medullary tissue or fetal substantia nigra has been transplanted to the caudate nucleus, in the belief that the transplanted tissue can continue to synthesize and release dopamine. Results from preliminary studies have been contradictory, and this approach is highly controversial. The precise mechanism of benefit, if it occurs, is unclear.

H. Deep Brain Stimulation. High-frequency thalamic stimulation is effective for the relief of parkinsonian tremor. Pallidal stimulation is currently under study as an alternative to pallidotomy in patients with other parkinsonian deficits, as is deep brain stimulation at other sites. This approach has the advantage of being reversible and causing minimal or no damage to the brain.

I. Physical Therapy and Aids for Daily Living. Physical therapy and speech therapy are beneficial to many patients with parkinsonism, and the quality of life can often be improved by providing simple aids to daily living. Such aids may include extra rails or banisters placed strategically about the home for additional support, table cutlery with large handles, nonslip rubber table mats,

devices to amplify the voice, and chairs that will gently eject the occupant at the push of a button.

PROGRESSIVE SUPRANUCLEAR PALSY

Progressive supranuclear palsy is an idiopathic degenerative disorder that primarily affects subcortical gray matter regions of the brain. The principal neuropathologic finding is neuronal degeneration with the presence of neurofibrillary tangles in the midbrain, pons, basal ganglia, and dentate nuclei of the cerebellum. Associated neurochemical abnormalities include decreased concentrations of dopamine and its metabolite homovanillic acid in the caudate nucleus and putamen. The classic clinical features are supranuclear ophthalmoplegia, pseudobulbar palsy, axial dystonia with or without extrapyramidal rigidity of the limbs, and dementia. Men are affected twice as often as women, and the disorder has its onset between ages 45 and 75 years.

Supranuclear ophthalmoplegia is characterized by prominent failure of voluntary vertical gaze, with later paralysis of horizontal gaze; oculocephalic and oculovestibular reflexes are preserved. Postural instability and unexplained falls also occur early. In addition, the neck often assumes an extended posture (axial dystonia in extension), with resistance to passive flexion. Rigidity of the limbs and bradykinesia may mimic Parkinson's disease, but tremor is rare. A coexisting pseudobulbar palsy produces facial weakness, dysarthria, dysphagia, and often exaggerated jaw jerk and gag reflexes; there may also be exaggerated and inappropriate emotional responses (pseudobulbar affect). Hyperreflexia, extensor plantar responses, and cerebellar signs are sometimes seen. The dementia of progressive supranuclear palsy is characterized by forgetfulness, slowed thought processes, alterations of mood and personality, and impaired calculation and abstraction. Focal cortical dysfunction is rare.

Parkinson's disease differs in that voluntary downward and horizontal gaze are not usually lost, axial posture tends to be characterized by flex ion rather than extension, tremor is common, the course is less fulminant, and antiparkinsonian medications are more often effective.

Dopaminergic preparations are occasionally of benefit for rigidity and bradykinesia. Anticholinergics such as amitriptyline, 50-75 mg orally at bedtime, or benztropine, 6-10 mg/d orally, have been reported to improve speech, gait, and pathologic laughing or crying, and methysergide, 8-12 mg/d orally, may ameliorate dysphagia. There is no treatment for the dementia.

The disorder typically follows a progressive course, with death from aspiration or inanition within 2-12 (usually 4-7) years.

CORTICAL BASAL GANGLIONIC DEGENERATION

Cortical basal ganglionic degeneration is a rare, nonfamilial, degenerative disorder of unknown cause that occurs in middle-aged or elderly persons of either sex. It sometimes simulates Parkinson's disease when bradykinesia and rigidity are conspicuous features. Postural-action tremor may also occur, but the usual cause of profound disability is apraxia and clumsiness rather than extrapyramidal deficits. Other features of the established disorder include speech disturbances (aphasic, apraxic, or dysarthric), cortical sensory deficits (such as neglect syndromes), stimulus-sensitive myoclonus, dysphagia, postural disturbances, dystonic features, and ultimately cognitive decine and behavioral changes. Frontal release signs, brisk tendon reflexes, and extensor plantar responses may also be encountered.

The disorder is distinguished from Parkinson's disease by the marked apraxia that often leads to a useless limb, difficulty in opening or closing the eyes, or speech disturbances. The presence of pyramidal and cortical deficits in addition to any extrapyramidal dysfunction and the relative preservation of cognitive function, at least until late in the course of the disorder, also help in this regard, but definitive diagnosis can be made only at autopsy.

Antiparkinsonian medication is generally unhelpful but is certainly worthy of trial. No specific therapy exists.

The disorder follows a progressive course, leading to increasing disability and dependence. Death typically follows within 10 years, often sooner, from aspiration pneumonia.

HUNTINGTON'S DISEASE

Huntington's disease, characterized by the gradual onset and subsequent progression of chorea and dementia, is a hereditary disorder of the nervous system that has been traced to a single gene defect on the short arm of chromosome 4; there is an expanded and unstable CAG trinucleotide repeat at 4p16.3. The disorder is inherited in an autosomal dominant manner, so that the offspring of an affected patient have a 50% chance of developing the disorder. In the few homozygous cases that have been identified, the clinical features are identical to those seen in heterozygotes. Huntington's disease occurs throughout the world and in all ethnic groups. Its prevalence rate is about 5 per 100,000 population. Symptoms usually do not appear until adulthood (typically between 30 and 50 years of age), by which time these patients have often started families of their own; thus, the disease continues from one generation to the next.

Pathogenesis

The manner in which the Huntington gene produces its devastating consequences is unknown. Postmortem examination of patients with the disease reveals cell loss, particularly in the cerebral cortex and corpus striatum. In the latter region, medium-sized spiny neurons that contain γ-aminobutyric acid (GABA) and enkephalin and project to the external segment of the globus pallidus are affected earliest, but other classes of neurons are eventually involved as well. Biochemical studies have shown that the concentrations of the inhibitory neurotransmitter GAB A, its biosynthetic enzyme glutamic acid decarboxylase (GAD), and acetylcholine and its biosynthetic enzyme choline acetyltransferase are all reduced in the basal ganglia of patients with Huntington's disease. The concentration of dopamine is normal or slightly increased. Changes in the concentrations of neuropeptides in the basal ganglia have also been found, including decreased substance P, methionine enkephalin, dynorphin, and cholecystokinin and increased somatostatin and neuropeptide Y. Neurons containing NADPH diaphorase activity are spared. Positron emission tomography has shown reduced glucose utilization in an anatomically normal caudate nucleus.

Clinical Findings

Symptoms usually begin in the fourth or fifth decade, and the disease is progressive, with an average life span after onset of about 15 years.

A. Initial Symptoms. Either abnormal movements or intellectual changes may be the initial symptom, but ultimately both are present.

1. Dementia. The earliest mental changes often consist of irritability, moodiness, and antisocial behavior, but a more obvious dementia subsequently develops.

2. **Chorea**. Movement disturbance may be characterized initially by no more than an apparent fidgetiness or restlessness, but grossly abnormal choreiform movements are eventually seen.

3. Atypical forms. Especially in cases developing during childhood-but occasionally in adult-onset cases as well-the clinical picture is dominated by progressive rigidity and akinesia, with little or no chorea. This is known as the Westphal variant, and the correct diagnosis is suggested by the accompanying dementia and positive family history.

Epilepsy and cerebellar ataxia are frequent features of the juvenile form but not of adult cases.

B. Family History. In cases where a positive family history cannot be obtained, it must be remembered that the early death of a parent may make the history incomplete and that relatives often conceal the familial nature of the disorder. In addition, a certain degree of eccentric behavior, clumsiness, or restlessness may be regarded as normal by lay people and medical personnel unfamiliar with the disorder. The family history cannot therefore be regarded as negative

until all close relatives of the patient have been examined by the physician personally. Nevertheless, apparently sporadic cases are occasionally encountered.

C. Genetic Testing. Genetic testing now provides an accurate and definitive means of establishing the diagnosis and also permits the presymptomatic detection of the disease.

D. Imaging. CT scanning or MRI often demonstrates atrophy of the cerebral cortex and caudate nucleus in established cases.

Differential Diagnosis

Drug-induced chorea, which is most common, can usually be identified from the history. Laboratory studies can exclude most medical disorders associated with chorea. Other hereditary disorders in which chorea is a conspicuous feature are described below.

Benign hereditary chorea is a recently recognized disorder that is inherited in either an autosomal dominant or recessive manner and is characterized by choreiform movements that develop in early childhood, do not progress during adult life, and are not associated with dementia.

Familial chorea sometimes occurs in association with circulating acanthocytes (spiny red blood cells), but examination of a wet blood film will clearly distinguish this disorder. Other clinical features of chorea-acanthocytosis include orolingual ticlike dyskinesias, vocalizations, mild intellectual decline, seizures, peripheral neuropathy, and muscle atrophy. Parkinsonian features are sometimes present. Unlike certain other disorders associated with circulating acanthocytes, there is no disturbance of ~-lipoprotein concentration in the peripheral blood.

Paroxysmal choreoathetosis may occur on a familial basis, but the intermittent nature of the symptoms and their relationship to movement or emotional stress usually distinguish this disorder from Huntington's disease.

The age at onset of symptoms usually distinguishes Huntington's disease from certain rare inherited childhood disorders characterized by choreoathetosis. Wilson's disease can be distinguished from Huntington's disease by the mode of inheritance, the presence of Kayser-Fleischer rings, and abnormal serum copper and ceruloplasmin levels.

When the early symptoms constitute progressive intellectual failure, it may not be possible to distinguish Huntington's disease from other varieties of dementia unless the family history is characteristic or the movement disorder becomes noticeable.

Treatment & Prognosis

There is no cure for Huntington's disease, which, as a rule, terminates fatally 10-20 years after clinical onset. There is no treatment for the dementia, but the movement disorder may respond to drugs that interfere with dopaminergic inhibition of striatal output neurons. These include dopamine D2-receptor-

blocking drugs such as haloperidol, 0.5-4 mg orally four times daily, or chlorpromazine, 25-50 mg orally three times daily; and drugs that deplete dopamine from nerve terminals, such as reserpine, 0.5-5 mg/d orally, or tetrabenazine 12.5-50 mg orally three times daily. Drugs that potentiate GABAergic or cholinergic neurotransmission are generally ineffective.

Patients should be advised of the risk of transmitting the disease, and living offspring should receive genetic counseling. Genetic markers for detection of presymptomatic Huntington's disease should be used.

SYDENHAM'S CHOREA

This disorder occurs principally in children and adolescents as a complication of a previous group A hemolytic streptococcal infection. The underlying patho10gic feature is probably arteritis. In about 30% of cases, it appears 2 or 3 months after an episode of rheumatic fever or polyarthritis, but in other patients no such history can be obtained. There is usually no recent history of sore throat and no fever. The disorder may have an acute or insidious onset, usually subsiding within the following 4-6 months. It may recur during pregnancy, however, or in patients taking oral contraceptive preparations.

Sydenham's chorea is characterized by abnormal choreiform movements that are sometimes unilateral and, when mild, may be mistaken for restlessness or fidgetiness. There may be accompanying behavioral changes, with the child becoming irritable or disobedient. Obsessive-compulsive symptoms and emotionallability also occur. In 30% of cases there is evidence of cardiac involvement, but the sedimentation rate and antistreptolysin 0 titer are usually normal. The traditional treatment is bed rest, sedation, and prophylactic antibiotic therapy even if there are no other signs of acute rheumatism. A course of intramuscular penicillin is generally recommended, and continuous prophylactic oral penicillin daily until about age 20 years is also frequently advised to prevent streptococcal infections. The prognosis is essentially that of the cardiac complications.

IDIOPATHIC TORSION DYSTONIA

This disorder is characterized by dystonic movements and postures and an absence of other neurologic signs. The birth and developmental histories are normal. Before the diagnosis can be made, other possible causes of dystonia must be excluded on clinical grounds and by laboratory investigations.

Idiopathic torsion dystonia may be inherited as an autosomal dominant, autosomal recessive, or X-linked recessive disorder, and the defective genes have been localized in some cases. Molecular genetic techniques permit identifi-

cation of carriers of the gene for the dominantly inherited disorder, which has been identified and is named DYT1. Other cases seem to occur on a sporadic basis. Changes in the concentrations of norepinephrine, serotonin, and dopamine have been demonstrated in a variety of brain regions, but their role in the pathogenesis of dystonia is uncertain. Onset may be in childhood or later life, and this disorder remains as a lifelong affliction. The diagnosis is made on clinical grounds.

Clinical Findings

A. History. When onset is in childhood, a family history is usually obtainable. Symptoms generally commence in the legs. Progression is likely, and it leads to severe disability from generalized dystonia.

With onset in adult life, a positive family history is not likely to be obtained. The initial symptoms are usually in the arms or axial structures. Generalized dystonia may ultimately develop in about 20% of patients with adult-onset dystonia, but severe disability does not usually occur.

B. Examination. The disorder is characterized by abnormal movements and postures that are typically exacerbated by voluntary activity. For example, the neck may be twisted to one side (torticollis), the arm held in a hyperpronated position with the wrist flexed and fingers extended, the leg held extended with the foot plantar-flexed and inverted, or the trunk held in a flexed or extended position. There is often facial grimacing, and other characteristic facial abnormalities may also be encountered, including blepharospasm (spontaneous, involuntary forced closure of the eyelids for a variable period of time) and oromandibular dystonia. This consists of spasms of the muscles about the mouth, causing, for example, involuntary opening or closing of the mouth; pouting, pursing, or retraction of the lips; retraction of the platysma muscle; and roving or protruding movements of the tongue.

Differential Diagnosis

It is important to exclude other causes of dystonia before a diagnosis of idiopathic torsion dystonia is made. A normal developmental history prior to the onset of abnormal movements, together with the absence of other neurologic signs and normal results of laboratory investigations, is important in this regard.

Treatment

The abnormal movements may be helped, at least in part, by drugs. A dramatic response to levodopa suggests a variant of classic torsion dystonia, discussed separately below. Anticholinergic drugs given in the highest doses that can be tolerated (typically, trihexyphenidyl, 40-50 mg/d orally in divided doses) may be very effective. Diazepam is occasionally helpful. Phenothiazines, haloperidol, or tetrabenazine may be worthwhile; however, at effective doses, these drugs usually lead to a mild parkinsonian syndrome. Other drugs that are some-

times helpful are baclofen and carbamazepine. Stereotactic thalamotomy may help patients with predominantly unilateral dystonia that particularly involves the limbs. If all cases are considered together, about one-third of patients eventually become so severely disabled that they are confined to chair or bed, while another one-third are affected only mildly. In general, severe disability is more likely to occur when the disorder commences in childhood.

Dopa-responsive dystonia

Inherited in an autosomal dominant manner, the gene causing this disorder maps to chromosome 14q. Symptom onset is typically in childhood but may occur later. Girls are affected more commonly than boys. Disabling dystonia is accompanied by bradykinesia and rigidity that may lead to a mistaken diagnosis of juvenile Parkinson's disease. Remarkable recovery occurs with low doses of levodopa, to which patients are particularly sensitive.

FOCAL TORSION DYSTONIA

A number of the dystonic features of idiopathic torsion dystonia may also occur as isolated phenomena. They are probably best regarded as focal dystonias that occur as formes frustes of idiopathic torsion dystonia in patients with a positive family history or that represent a focal manifestation of its adult-onset form when there is no family history.

Both **blepharospasm** and **oromandibular dystonia** can occur as isolated focal dystonias.

Spasmodic torticollis usually begins in the fourth or fifth decade and is characterized by a tendency for the neck to twist to one side. This often occurs episodically in early stages, but eventually the neck is held continuously to one side. Although the disorder is usually lifelong once it develops, spontaneous remission does occur occasionally, especially in the first 18 months after onset. Medical treatment is generally unsatisfactory. A trial of the drugs used in treating idiopathic torsion dystonia is worthwhile, since some patients do obtain undoubted benefit. Selective section of the spinal accessory nerve (cranial nerve XI) and the upper cervical nerve roots is sometimes helpful for patients in whom the neck is markedly deviated to the side, but recurrence of the abnormal posture is frequent. Local injection of botulinum toxin into the overactive muscles may also produce benefit for up to several months; it can be repeated as needed. It is the most effective treatment available for this disorder.

Writer's cramp is characterized by dystonic posturing of the hand and forearm when the hand is used for writing and sometimes other tasks such as playing the piano or using a screwdriver or table cutlery.

Drug treatment is usually unrewarding, and it is often necessary for patients to learn to use the other hand for these tasks. Injections of botulinum toxin into the involved muscles are sometimes helpful.

WILSON'S DISEASE

Wilson's disease is an autosomal recessive disorder of copper metabolism that produces neurologic and hepatic dysfunction. The gene localizes in the region of chromosome 13q14-21, but the disease is caused by a number of different mutations, two of which are encountered fairly frequently in affected patients. While the precise nature of the biochemical abnormality in Wilson's disease is unknown, its pathogenesis appears to involve decreased binding of copper to the transport protein ceruloplasmin. As a result, large amounts of unbound copper enter the circulation and are subsequently deposited in tissues, including the brain, liver, kidney, and cornea.

Clinical Findings

A. Mode of Presentation. Wilson's disease usually presents in childhood or young adult life. The average age at onset is about 11 years for patients presenting with hepatic dysfunction and 19 years for those with initial neurologic manifestations, but the disease may begin as late as the sixth decade. Hepatic and neurologic presentations are about equally common, and most patients, if untreated, eventually develop both types of involvement. Rare presentations include joint disease, fever, hemolytic anemia, and behavioral disturbances.

B. Nonneurologic Findings. Ocular and hepatic abnormalities are the most prominent nonneurologic manifestations of Wilson's disease. The most common ocular finding is Kayser-Fleischer rings: bilateral brown corneal rings that result from copper deposition in Descemet's membrane. The rings are present in virtually all patients with neurologic involvement but may be detectable only by slit lamp examination. Hepatic involvement leads to chronic cirrhosis, which may be complicated by splenomegaly, esophageal varices with hematemesis, or fulminant hepatic failure. Splenomegaly may cause hemolytic anemia and thrombocytopenia.

C. Neurologic Findings. Neurologic findings in Wilson's disease reflect the disproportionate involvement of the caudate nucleus, putamen, cerebral cortex, and cerebellum. Neurologic signs include resting or postural tremor, choreiform movements of the limbs, facial grimacing, rigidity, hypokinesia, dysarthria, dysphagia, abnormal (flexed) postures, and ataxia. Seizures may also occur. Psychologic disorders in Wilson's disease include dementia, characterized by mental slowness, poor concentration, and memory impairment; disorders of affect, behavior, or personality; and (rarely) psychosis with hallucinations. There

is a tendency for a dystonic or parkinsonian picture with hyperreflexia and extensor plantar responses to predominate when the disease begins before age 20 yearsand for older patients to exhibit wild tremor, chorea, or ballismus. Symptoms may progress rapidly, especially in younger patients, but are more often gradual in development with periods of remission and exacerbation.

Differential Diagnosis

When Wilson's disease presents as a neurologic disorder, other conditions that must be considered in the differential diagnosis include multiple sclerosis and juvenile-onset Huntington's disease.

Investigative Studies

Investigation may reveal abnormal liver function blood tests and aminoaciduria as a result of renal tubular damage. The levels of serum copper and ceruloplasmin (an α_2-globulin to which 90% of the circulating copper is bound) are low, and 24-hour urinary copper excretion is generally increased. Liver biopsy reveals a huge excess of copper; it also usually reveals cirrhosis. Brain CT scanning or MRI may show cerebrocortical atrophy and abnormalities in the basal ganglia.

Treatment

Wilson's disease is treated with penicillamine, a copper-chelating agent that promotes extraction of copper from tissue deposition sites. Treatment should be started as early as possible and customarily employs 1.5-2 g/d of orally administered penicillamine. The response to treatment may take several months and can be monitored by serial slit lamp examinations and blood chemistries. Side effects of penicillamine include nausea, nephrotic syndrome, myasthenia gravis, arthropathy, pemphigus, diverse blood dyscrasias, and a lupuslike syndrome; moreover, penicillamine may cause an additional worsening of neurologic symptoms. Treatment with tetrathiomolybdate is sometimes helpful. Restriction of dietary copper and administration of zinc sulfate (200 mg/d orally) can decrease copper absorption. Treatment must be continued for the lifetime of the patient, and most patients treated early can expect a complete or nearly complete recovery.

Siblings of affected patients should be screened for presymptomatic Wilson's disease with neurologic and slit lamp examinations and determination of serum ceruloplasmin levels. If no abnormalities are found, serum copper and urinary copper excretion should be assayed and liver biopsy performed if necessary. If these investigations reveal preclinical Wilson's disease, therapy should be instituted as described above for symptomatic disease.

DRUG-INDUCED MOVEMENT DISORDERS

Parkinsonism

Parkinsonism frequently complicates treatment with dopamine-depleting agents such as reserpine or antipsychotic dopamine-receptor antagonists such as phenothiazines or butyrophenones. In the case of antipsychotic drugs, the risk of this complication is greatest when agents are used that are potent D_2-receptor antagonists with little anticholinergic effect, such as piperazine phenothiazines, butyrophenones, and thioxanthenes. In addition, women and elderly patients appear to be at somewhat increased risk. Tremor is relatively uncommon, while hypokinesia tends to be symmetric and the most conspicuous neurologic feature of parkinsonism. These points, together with the history of drug ingestion, often point to the iatrogenic nature of the disorder. Signs usually develop within 3 months after starting the offending drug and disappear over weeks or months following discontinuance.

Depending on the severity of symptoms and the necessity for continuing antipsychotic drug therapy, several strategies are available for treating drug-induced parkinsonism. These include discontinuing the antipsychotic drug, substituting a less potent dopamine receptor antagonist, or adding an anticholinergic drug such as trihexyphenidyl or benztropine. Levodopa is of no help if the neuroleptic drugs are continued; it may be helpful if these drugs are discontinued but may aggravate the psychotic disorder for which they were originally prescribed.

Acute Dystonia or Dyskinesia

Acute dystonia or dyskinesia (such as blepharospasm, torticollis, or facial grimacing) is an occasional complication of dopamine receptor antagonist treatment, generally occurring within 1 week after introduction of such medication and often within 48 hours. Men and younger patients show increased susceptibility to this complication. The pathophysiologic basis of the disturbance is unclear, but intravenous treatment with an anticholinergic drug (eg, benztropine, 2 mg, or diphenhydramine, 50 mg) usually alleviates it.

Akathisia

Akathisia is a state of motor restlessness characterized by an inability to sit or stand still, which is relieved by moving about. It is a very common movement disorder induced by chronic treatment with antipsychotic drugs and occurs more often in women than in men. Akathisia is treated in the same manner as drug-induced parkinsonism.

Tardive Dyskinesia

Tardive dyskinesia may develop after long-term treatment with antipsychotic (dopamine-receptor-antagonist) drugs. It is commonly encountered in chronically institutionalized psychiatric patients, and the risk of developing tardive dyskinesia appears to increase with advancing age. The manner in which chronic drug treatment promotes a movement disorder is unknown.

Drug-induced supersensitivity of striatal dopamine receptors has been proposed but is unlikely to be responsible for several reasons. Supersensitivity always accompanies chronic antipsychotic drug treatment, whereas tardive dyskinesia does not. Supersensitivity may occur early in the course of treatment, while tardive dyskinesia does not develop for at least 3 months. In addition supersensitivity is invariably reversible when drugs are discontinued; tardive dyskinesia is not. The clinical features of tardive dyskinesia, particularly its persistent nature, are more suggestive of an underlying structural abnormality. Such an abnormality may involve GABA-neurons, because GABA and its synthesizing enzyme, glutamic acid decarboxylase, are depleted in the basal ganglia following chronic treatment of animals with antipsychotic drugs and GABA levels in CSF are decreased in patients with tardive dyskinesia. No consistent pathologic features have been found in the brains of patients with tardive dyskinesia, although inferior olive atrophy, degeneration of the substantia nigra, and swelling of large neurons in the caudate nucleus have been described in some cases. The clinical disorder is characterized by abnormal choreoathetoid movements that are often especially conspicuous about the face and mouth in adults and tend to be more obvious in the limbs in children. The onset of dyskinesia is generally not until months-or years-after the start of treatment with the responsible agent. Tardive dyskinesia may be impossible to distinguish from such disorders as Huntington's disease or idiopathic torsion dystonia unless a history of drug exposure is obtained.

Tardive dyskinesia is easier to prevent than to cure. Antipsychotic drugs should be prescribed only on clear indication, and their long-term use should be monitored, with periodic drug holidays to determine whether the need for treatment continues. Drug holidays may also help to unmask incipient dyskinesias – which, curiously, tend to worsen when the drug is withdrawn. Antipsychotic medication should be stopped if possible when dyskinesia appears during a drug holiday, for in such circumstances the abnormal movements occasionally will remit.

Treating the established disorder is generally unsatisfactory, though it sometimes resolves spontaneously, especially in children or young adults. Antidopaminergic agents such as haloperidol or phenothiazines suppress the abnormal movements, but their use for this purpose is not recommended since they may aggravate the underlying disorder. Treatment with reserpine, 0.25 mg

gradually increased to 2-4 mg/d orally, or tetrabenazine 12.5 mg gradually increased to as much as 200 mg/d orally, may be helpful. Both these drugs deplete monoamine neurotransmitters, including dopamine. A number of other pharmacologic approaches have been suggested, but there are conflicting reports regarding their utility.

A variety of other late and often persistent movement disorders may appear during the course of antipsychotic drug treatment. **Tardive dystonia** is usually segmental (affecting two or more contiguous body parts, such as the face and neck or arm and trunk) in nature. It is less often focal; when this is the case, the head and neck are particularly apt to be affected, producing blepharospasm, torticollis, or oromandibular dystonia. Generalized dystonia is least common and tends to occur in younger patients. Treatment is with tetrabenazine (if available) as described for tardive dyskinesia or with anticholinergic drugs as described earlier for idiopathic torsion dystonia. **Tardive akathisia** can also occur; it is treated in the same manner as drug-induced parkinsonism. **Tardive tic,** a drug-induced disorder resembling Gilles de la Tourette's syndrome (see later), is characterized by multifocal motor and vocal tics and can be similarly treated with clonidine (as described later) if symptoms do not remit spontaneously.

Neuroleptic Malignant Syndrome

This rare complication of treatment with antipsychotic drugs (neuroleptics) is manifested by rigidity, fever, altered mental status, and autonomic dysfunction. Haloperidol is implicated most often, but the syndrome can complicate treatment with any antipsychotic drug; whether concomitant treatment with lithium or anticholinergic drugs increases the risk is uncertain. Symptoms typically develop over 1-3 days and can occur at any time during the course of treatment. The differential diagnosis includes infection, which must be excluded in any febrile patient. Neuroleptic malignant syndrome resembles malignant hyperthermia, but the latter disorder develops over minutes to hours rather than days and is associated with the administration of inhalational anesthetics or neuromuscular blocking agents rather than antipsychotics. Treatment of neuroleptic malignant syndrome includes withdrawal of antipsychotic drugs, lithium, and anticholinergics; reduction of body temperature with antipyretics and artificial cooling; and rehydration. Dantrolene may be beneficial, as may bromocriptine, levodopa preparations, or amantadine. The mortality rate is as high as 20%.

Other Drug-Induced Movement Disorders

Levodopa produces a wide variety of abnormal movements as a dose-related phenomenon in patients with parkinsonism. They can be reversed by withdrawing the medication or reducing the dose. Chorea may also develop in patients receiving bromocriptine, anticholinergic drugs, phenytoin, carba-

mazepine, amphetamines, lithium, and oral contraceptives; it resolves with discontinuance of the responsible drug. Dystonia has resulted from administration of bromocriptine, lithium, carbamazepine, and metoclopramide; and postural tremor from administration of theophylline, caffeine, lithium, thyroid hormone, tricyclic antidepressants, valproic acid, and isoproterenol.

GILLES DE LA TOURETTE'S SYNDROME

Gilles de la Tourette's syndrome, characterized by chronic-typically life-long-multiple motor and verbal tics, is of unknown cause and does not relate to social class, ethnic group, perinatal abnormalities, birth trauma, or birth order. Symptoms begin before 21 years of age, and the course is one of remission and relapse. Most cases are sporadic, although there is occasionally a family history, and partial expression of the trait may occur in siblings or offspring of patients. Inheritance has been attributed to an autosomal dominant gene with variable penetrance. Males are affected more commonly than females. The prevalence in the United States has been estimated to be 0.05%.

The pathophysiology is obscure. Dopaminergic excess in the brains of patients with Gilles de la Tourette's syndrome has been postulated, mainly because of the beneficial effects that dopamine-blocking drugs can have on the tics. The administration of dopamine receptor agonists often fails to produce the exacerbation of symptoms that might be anticipated from this hypothesis, however. No structural basis for the clinical disorder has been recognized.

Clinical Findings

Symptoms usually commence between ages 2 and 21 years. The first signs consist of motor tics in 80% of cases and vocal tics in 20%; there may be either a single tic or multiple tics. When the initial sign is a motor tic, it most commonly involves the face, taking the form of sniffing, blinking, forced eye closure, etc. It is generally not possible to make the diagnosis at this stage.

All patients ultimately develop a number of different motor tics and involuntary vocal tics, the latter commonly consisting of grunts, barks, hisses, throat-clearing or coughing, and the like, and sometimes taking the form of verbal utterances including coprolalia (vulgar or obscene speech). There may also be echolalia (parroting the speech of others), echopraxia (imitation of others' movements), and palilalia (repetition of words or phrases). The tics vary over time in severity, character, and the muscle groups involved. In 40-50% of cases, some of the tics involve self-mutilation with such activities as severe nail-biting or hair-pulling, picking at the nose, or biting the lips or tongue. Sensory tics, consisting of pressure, tickling, and warm or cold sensations, also occur. Behavioral disorders, including obsessive-compulsive disorder and attention deficit

hyperactivity disorder, are common in patients with Gilles de la Tourette's syndrome, but their precise relationship to the tic disorder is uncertain. Physical examination usually reveals no other abnormalities, but there is a higher than expected incidence of left-handedness or ambidexterity.

Differential Diagnosis

The differential diagnosis includes the various movement disorders that can present in childhood. Other disorders characterized by tics are distinguished by resolution of the tics by early adulthood or by the restricted number of tics.

Wilson's disease can simulate Gilles de la Tourette's syndrome; it must be excluded because it responds well to medical treatment. In addition to a movement disorder, Wilson's disease produces hepatic involvement, Kayser-Fleischer corneal rings, and abnormalities of serum copper and ceruloplasmin, which are absent in Gilles de la Tourette's syndrome.

Sydenham's chorea can be difficult to recognize if there is no recent history of rheumatic fever or polyarthritis and no clinical evidence of cardiac involvement, but this disorder is a self-limiting one, usually clearing in 3-6 months.

Bobble-head syndrome, which can be difficult to distinguish from Gilles de la Tourette's syndrome, is characterized by rapid, rhythmic bobbing of the head in children with progressive hydrocephalus.

Complications

Gilles de la Tourette's syndrome is often unrecognized for years, the tics being attributed to psychiatric illness or mistaken for some other form of abnormal movement. Indeed, in many cases the correct diagnosis is finally made by the family rather than the physician. In consequence, patients are often subjected to unnecessary and expensive treatment before the true nature of the disorder is recognized. Psychiatric disturbances, sometimes culminating in suicide, may occur because of the cosmetic and social embarrassment produced by the tics. Drug therapy can lead to a number of side effects.

Treatment

Treatment is symptomatic and, if effective, must be continued indefinitely. Clonidine has been reported to ameliorate motor or vocal tics in roughly 50% of children so treated. It may act by reducing activity in noradrenergic neurons arising in the locus ceruleus. It is started in a dose of 2-3 μg/kg/d, increasing after 2 weeks to 4 μg/kg/d and then, if necessary, to 5 μg/kg/d. It may cause an initial transient fall in blood pressure. The most frequent side effect is sedation. Other adverse reactions include reduced or excessive salivation and diarrhea.

Haloperidol is often effective. It is started at a low daily dose (0.25 mg), which is gradually increased by 0.25 mg every 4 or 5 days until there is maximum benefit with a minimum of side effects or until side effects limit further increments. A total daily dose of 2-8 mg is usually optimal, but higher doses are sometimes necessary. Side effects include extrapyramidal movement disorders, sedation, dryness of the mouth, blurred vision, and gastrointestinal disturbances. Pimozide, another dopaminergic-receptor antagonist, may be helpful in patients who are either unresponsive to or cannot tolerate haloperidol, but the longterm safety of pimozide is unknown. Treatment is started with 1 mg/d and the dose increased by 2 mg every 10 days; most patients require 7-16 mg/d. Phenothiazines such as fluphenazine may help, but patients who are unresponsive to haloperidol usually fail with these drugs as well.

Patients occasionally respond favorably to clonazepam or carbamazepine, but diazepam, barbiturates, tricyclic antidepressants, phenytoin, and cholinergic agonists (such as deanol) are usually not helpful.

RESTLESS LEGS SYNDROME

Restless legs syndrome is characterized by an unpleasant creeping discomfort that is perceived as arising deep within the legs and occasionally in the arms as well. Such symptoms tend to occur when patients are relaxed, especially while lying down or sitting, and lead to a need to move about. They are often particularly troublesome at night and may delay the onset of sleep. A sleep disorder associated with periodic movements during sleep may also occur and can be documented by polysomnographic recording. The cause is unknown, although the disorder seems especially common among pregnant women and is not uncommon among uremic or diabetic patients with neuropathy. Most patients, however, have no obvious predisposing cause. Symptoms sometimes resolve following correction of coexisting iron-deficiency anemia, and they may respond to treatment with drugs such as levodopa, bromocriptine, diazepam, clonazepam, or opiates. When opiates are required, those with long half-lives or low addictive potential should be used.

MYASTHENIA GRAVIS

Myasthenia gravis can occur at any age and is sometimes associated with thymic tumor, thyrotoxicosis, rheumatoid arthritis, or disseminated lupus erythematosus. More common in females than males, it is characterized by fluctuating weakness and easy fatigability of voluntary muscles; muscle activity cannot be maintained, and initially powerful movements weaken readily. There is a predilection for the external ocular muscles and certain other cranial muscles, including the masticatory, facial, pharyngeal, and laryngeal muscles. Respiratory and limb muscles may also be affected. Weakness is due to a variable block of neuromuscular transmission related to an immune-mediated decrease in the number of functioning acetylcholine receptors. A similar disorder in patients receiving penicillamine for rheumatoid arthritis frequently remits when the drug is discontinued.

Clinical Findings

Although the onset of the disease is usually insidious, the disorder is sometimes unmasked by a concurrent infection, which leads to an exacerbation of symptoms. Exacerbations may also occur in pregnancy or before menses. Symptoms may be worsened by quinine, quinidine, procainamide, propranolol, phenytoin, lithium, tetracycline, and aminoglycoside antibiotics, which should therefore be avoided in such patients. Myasthenia follows a slowly progressive course. Patients present with ptosis, diplopia, difficulty in chewing or swallowing, nasal speech, respiratory difficulties, or weakness of the limbs. These symptoms often fluctuate in intensity during the day, and this diurnal variation is superimposed on longer-term spontaneous relapses and remissions that may last for weeks.

Clinical examination confirms the weakness and fatigability of affected muscles. The weakness does not conform to the distribution of any single nerve, root, or level of the central nervous system. In more than 90% of cases the extraocular muscles are involved, leading to often asymmetric ocular palsies and ptosis. Pupillary responses are not affected. The characteristic feature of the disorder is that sustained activity of affected muscles leads to temporarily increased weakness. Thus, sustained upgaze for 2 minutes can lead to increased ptosis, with power in the affected muscles improving after a brief rest. In advanced cases, there may be some mild atrophy of affected muscles. Sensation is normal, and there are usually no reflex changes.

Diagnosis

The diagnosis of myasthenia gravis can generally be confirmed by the benefit that follows administration of anticholinesterase drugs: the power of affected muscles is influenced at a dose that has no effect on normal muscles and slight, if any, effect on muscles weakened by other causes.

The most commonly used pharmacological test is the edrophonium (Tensilon) test. Edrophonium is given intravenously in a dose of 10 mg (1 mL), of which 2 mg is given initially and the remaining 8 mg about 30 seconds later if the test dose is well tolerated. In myasthenic patients, there is an obvious improvement in the strength of weak muscles that lasts for about 5 minutes.

Alternatively, 1.5 mg of neostigmine can be given intramuscularly, with a response that lasts for about 2 hours; atropine sulfate (0.6 mg) should be available to counteract the muscarinic cholinergic side effects of increased salivation, diarrhea, and nausea. Atropine does not affect nicotinic cholinergic function at the neuromuscular junction. The longer-acting neostigmine reduces the incidence of false-negative evaluations.

Investigative Studies

X-rays and CT scans of the chest may reveal a coexisting thymoma. Impaired neuromuscular transmission can be detected electrophysiologically by a decremental response of muscle to repetitive supramaximal stimulation (at 2 or 3 Hz) of its motor nerve, but normal findings do not exclude the diagnosis. Single-fiber electromyography shows increased variability in the interval between two muscle fiber action potentials from the same motor unit in clinically weak muscles. Measuring serum acetylcholine receptor antibody levels is often helpful, since increased values are found in 80-90% of patients with generalized myasthenia gravis.

Treatment

Medications (referred to earlier) that impair neuromuscular transmission should be avoided. The following approaches to treatment are recommended.

A. Anticholinesterase Drugs. Treatment with these drugs provides symptomatic benefit without influencing the course of the underlying disease. The mainstay of treatment is pyridostigmine, at doses individually determined but usually between 30 and 180 mg (average, 60 mg) four times daily. The older drug neostigmine may still be used, in rare instances, by parenteral administration. Small doses of atropine may attenuate side effects such as bowel hypermotility or hypersalivation. Overmedication can lead to increased weakness, which, unlike myasthenic weakness, is unaffected or enhanced by intravenous edrophonium. Such a cholinergic crisis may be accompanied by pallor, sweating, nausea, vomiting, salivation, colicky abdominal pain, and miosis.

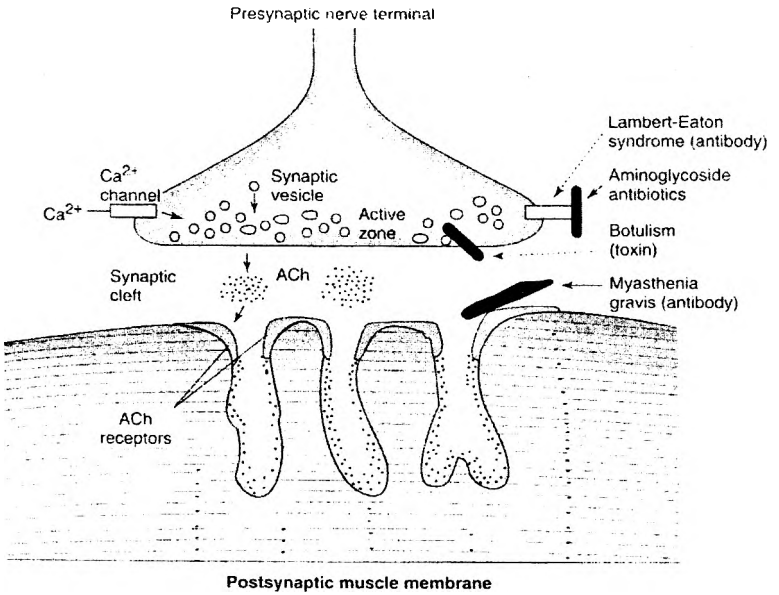


Fig. 19. Sites of involvement in disorders of neuromuscular transmission. At left, normal transmission involves depolarization-induced influx of calcium (Ca) through voltage-gated channels. This stimulates release of acetylcholine (ACh) from synaptic vesicles at the active zone and into the synaptic cleft. ACh binds to ACh receptors and depolarizes the postsynaptic muscle membrane. At right, disorders of neuromuscular transmission result from blockage of Ca channels (Lambert-Eaton syndrome or aminoglycoside antibiotics), impairment of Ca-mediated ACh release (botulinum toxin), or antibody-induced internalization and degradation of ACh receptors (myasthenia gravis). (From R. Simon, M. Aminoff, D. Greenberg, 1999)

B. Thymectomy. Thymectomy should be performed in patients under 60 years of age, and considered in those older, with weakness that is not restricted to the extraocular muscles. Although thymectomy usually leads to symptomatic benefit or remission, the mechanism by which it confers benefit is unclear, and its beneficial effect may not be evident immediately.

C. Corticosteroids. Corticosteroids are indicated for patients who have responded poorly to anticholinesterase drugs and have already undergone thymectomy. Treatment is initiated with the patient in the hospital, since weakness may initially be exacerbated. An initial high dose of prednisone (60-100 mg/d orally) can gradually be tapered to a relatively low maintenance level (5-15 mg/d) as improvement occurs. Alternate-day treatment is helpful in reducing the incidence of side effects.

D. Azathioprine. This drug can be used in patients with severe or progressive disease despite thymectomy and treatment with anticholinesterases and corticosteroids. It can also be given in place of high doses of corticosteroids to patients who show no sustained benefit with low doses. The usual dose is 2-3 mg/kg/d, increased from a lower initial dose.

E. Plasmapheresis. Plasmapheresis may be used to achieve temporary improvement in patients deteriorating rapidly or in myasthenic crisis, and in certain special circumstances, such as prior to surgery that is likely to produce postoperative respiratory compromise.

F. Intravenous Immunoglobulins. Intravenous immunoglobulins have also been used to provide temporary benefit in circumstances similar to those in which plasmapheresis is used.

Prognosis

Most patients can be managed successfully with drug treatment. The disease may have a fatal outcome because of respiratory complications such as aspiration pneumonia;

MYASTHENIC SYNDROME (LAMBERT-EATON SYNDROME)

This disorder has a well-recognized association with an underlying neoplasm and may occasionally be associated with such autoimmune diseases as pernicious anemia; occasionally no cause is found. In the paraneoplastic disorder, antibodies directed against tumor antigens cross-react with voltage-gated calcium channels involved in acetylcholine release, leading to a disturbance of neuromuscular transmission.

Clinically there is weakness, especially of the proximal muscles of the limbs. Unlike myasthenia gravis, however, the extraocular muscles are characteristically spared, and power steadily increases if a contraction is maintained. Autonomic disturbances, such as dry mouth, constipation, and impotence, may also occur.

The diagnosis is confirmed electrophysiologically by the response to repetitive nerve stimulation. There is a remarkable increase in the size of the muscle response to stimulation of its motor nerve at high rates – even in muscles that are not clinically weak. The presence of autoantibodies to the P/Q subtype of voltage-gated calcium channels, found on the presynaptic membrane of the neuromuscular junction, is highly sensitive and specific to the Lambert-Eaton syndrome of any etiology.

Immunosuppressive drug therapy (corticosteroids and azathioprine as described earlier for myasthenia gravis) and plasmapheresis or intravenous immunoglobulin therapy may lead to improvement. Guanidine hydrochloride, 25-50 mg/kg/d in three or four divided doses, is sometimes helpful in seriously disabled patients, but adverse effects of the drug include bone marrow suppression and renal failure. The response to treatment with anticholinesterase drugs such as pyridostigmine or neostigmine, alone or in combination with guanidine, is variable. 3,4-Diaminopyridine (investigational), at doses up to 25 mg orally four times daily, may improve weakness and autonomic dysfunction; paresthesia is a common side effect, and seizures may occur. The disease improves with treatment of the underlying condition.

MYOPATHIC DISORDERS

MUSCULAR DYSTROPHIES

The muscular dystrophies are a group of inherited myopathic disorders characterized by progressive muscle weakness and wasting. They are subdivided by their mode of inheritance, age at onset, distribution of involved muscles, rate of progression, and long-term outlook.

There is no specific treatment for the muscular dystrophies. It is important to encourage patients to lead as normal a life as possible. Deformities and contractures can often be prevented or ameliorated by physical therapy and orthopedic procedures. Prolonged bed rest must be avoided, as inactivity often leads to worsening of disability.

A. Duchenne's Dystrophy. The most common form of muscular dystrophy, it is an X-linked disorder that affects predominantly males. Symptoms begin by age 5 years, and patients are typically severely disabled by adolescence, with death occurring in the third decade. Toe walking, waddling gait, and an inability to run are early symptoms. Weakness is most pronounced in the proximal lower extremities but also affects the proximal upper extremities. In attempting to rise to stand from a supine position, patients characteristically must use their arms to climb up their bodies (Gowers' sign). Pseudohypertrophy of the calves caused by fatty infiltration of muscle is common. The heart is involved late in the course, and mental retardation is a frequent accompaniment. Serum CPK levels are exceptionally high.

No definitive treatment is available, but some studies suggest that prednisone, 1.5 mg/kg/d orally, may improve muscle strength in the short term (up to 6 months). Side effects include weight gain, cushingoid appearance, and hirsutism; the long-term effects of prednisone in this disorder are uncertain.

A genetic defect responsible for Duchenne's dystrophy has been identified and forms the basis of a diagnostic test. The gene in question is located on the short arm of the X chromosome and codes for the protein dystrophin, which is absent or profoundly reduced in muscle from patients with the disorder. The absence of dystrophin from synaptic regions of cerebral cortical neurons may contribute to mental retardation in patients with Duchenne's dystrophy. Gene therapy has not proven effective at this time for treating this muscular dystrophy.

B. Becker's Dystrophy. This is also X-linked and associated with a pattern of weakness similar to that observed in Duchenne's dystrophy. Its average onset (II years) and age at death (42 years) are later, however. Cardiac and cognitive impairment do not occur, and CPK levels are less strikingly elevated than in Duchenne's dystrophy. In contrast to Duchenne's dystrophy, dystrophin levels

in muscle are normal in Becker's dystrophy, but the protein is qualitatively altered.

C. Limb-Girdle Dystrophy. Previously a catchall designation that probably subsumed a variety of disorders, including undiagnosed cases of other dystrophies, it is (in classic form) inherited in autosomal recessive fashion, and in some affected families the defective gene has been localized to the long arm of chromosome 15. The disorder begins clinically between late childhood and early adulthood. In contrast to Duchenne's and Becker's dystrophies, the shoulder and pelvic girdle muscles are affected to a more nearly equal extent. Pseudohypertrophy is not seen, and CPK levels are less elevated.

D. Facioscapulohumeral Dystrophy. An autosomal dominant disorder that usually has its onset in adolescence, this is compatible with a normal life span. The genetic defect is a rearrangement of a homeobox gene localized to the telomere of the long arm of chromosome 4. The clinical severity of this condition is highly variable. Weakness is typically confined to the face, neck, and shoulder girdle, but foot drop can occur. Winged scapulae are common. The heart is not involved, and serum CPK levels are normal or only slightly elevated. Scapuloperoneal dystrophy is probably a variant, but genetic studies have shown linkage to chromosome 12 in some instances.

E. Distal myopathy. This autosomal dominant dystrophy typically presents after age 40, although onset may be earlier and symptoms more severe in homozygotes. Small muscles of the hands and feet, wrist extensors, and the dorsiflexors of the foot are affected. The precise pattern of involvement varies in the different subtypes of the disorder. The course is slowly progressive. Distal myopathies with autosomal recessive inheritance or occurring sporadically are also described and present with progressive leg weakness in adolescents or young adults.

F. Ocular Dystrophy. This is typically an autosomal dominant disorder, although recessive and sporadic cases also occur. Some cases are associated with deletions in mitochondrial DNA. Onset is usually before age 30 years. Ptosis is the earliest manifestation, but progressive external ophthalmoplegia subsequently develops; facial weakness is also common, and subclinical involvement of limb muscles may occur. The course is slowly progressive. The extent to which ocular dystrophy is distinct from oculopharyngeal dystrophy (see below) is unclear in many cases.

G. Oculopharyngeal Dystrophy. An autosomal dominant disorder, this is found with increased frequency in certain geographic areas, including Quebec and the southwestern United States. It most often begins in the third to fifth decade. Findings include ptosis, total external ophthalmoplegia, dysphagia, facial weakness, and often proximal limb weakness. CPK is mildly elevated. Dysphagia is particularly incapacitating and may require nasogastric feeding or gastrostomy.

H. Paraspinal Dystrophy. Progressive paraspinal weakness may develop after the age of 40 in patients of either gender, some of whom may have a family history of the disorder. Back pain and a marked kyphosis ("bent spine syndrome") are characteristic. The CPK is mildly elevated. CT scans show fatty replacement of paraspinal muscles.

MYOTONIC DISORDERS

In myotonia, an abnormality of the muscle fiber membrane (sarcolemma) leads to marked delay before the affected muscles can relax after a contraction; this leads to apparent muscle stiffness. In at least some cases, the disorder appears to be related to a decrease in chloride ion conductance across the sarcolemma. On examination, it is frequently possible to demonstrate myotonia by difficulty in relaxing the hand after sustained grip or by persistent contraction after percussion of the belly of a muscle. Electromyography of affected muscles may reveal characteristic high-frequency discharges of potentials that wax and wane in amplitude and frequency, producing over the EMG loudspeaker a sound like that of a dive bomber or chain-saw.

Myotonic Dystrophy

Myotonic dystrophy is a dominantly inherited disorder that usually is manifest in the third or fourth decade, although it may appear in early childhood. The gene defect is an expanded trinucleotide (CTG) repeat in a gene localized to the centromeric region of chromosome 19 (19cen-q13.2), and this expanded trinucleotide repeat forms the basis of a diagnostic test. The protein encoded by this gene has been designated myotonin-protein kinase. Occasional patients, however, have clinical features resembling myotonic dystrophy but no repeat expansion of the myotonin-protein kinase gene. Myotonia accompanies weakness and wasting of the facial, sternomastoid, and distal limb muscles. There may also be cataracts, frontal baldness, testicular atrophy, diabetes mellitus, cardiac abnormalities, and intellectual changes.

Myotonia can be treated with quinine sulfate, 300-400 mg three times daily; procainamide, 0.5-1 g four times daily; or phenytoin, 100 mg three times daily. In myotonic dystrophy, phenytoin is perhaps the drug of choice, since the other drugs may have undesirable effects on cardiac conduction. There is no treatment for the weakness that occurs, and pharmacologic maneuvers do not influence the natural history.

Myotonia Congenita

Myotonia congenita is usually inherited as a dominant trait that relates to a mutation on chromosome 7. Generalized myotonia without weakness is usually present from birth, but symptoms may not develop until early childhood.

Muscle stiffness is enhanced by cold and inactivity and relieved by exercise. Muscle hypertrophy, sometimes pronounced, is also a feature. A recessive form with later onset is associated with slight weakness and atrophy of distal muscles. Treatment with quinine sulfate, procainamide, tocainide, mexilitene, or phenytoin may help the myotonia.

TRAUMATIC BRAIN INJURY

Traumatic brain injury (TBI) continues to be an enormous public health problem, even with modern medicine in the 21st century. Most patients with TBI (75-80%) have mild head injuries; the remaining injuries are divided equally between the moderate and severe categories.

The cost to society of TBI is staggering, from both an economic and an emotional standpoint. Almost 100% of persons with severe head injury and as many as two thirds of those with moderate head injury will be permanently disabled and will not return to their premorbid level of function. In the United States, the direct cost of care for patients with TBI, excluding inpatient care, is estimated at more than $25 billion annually. The impact is even greater when one considers that most severe head injuries occur in adolescents and young adults.

Frequency

The annual incidence of TBI in some western countries has been estimated to be 180-220 cases per 100,000 population. In the United States, with a population of almost 300 million, approximately 600,000 new TBIs occur per year. As many as 10% of these injuries are fatal, resulting in almost 550,000 persons hospitalized annually with head injuries.

Etiology

While various mechanisms may cause TBI, the most common causes include motor vehicle accidents (collisions between vehicles, pedestrians struck by motor vehicles, bicycle accidents), falls, assaults, sports-related injuries, and penetrating trauma. Motor vehicle accidents account for almost half of the TBIs and in suburban/rural settings, they account for most TBIs. In cities with populations greater than 100,000, assaults, falls, and penetrating trauma are more common etiologies of head injury. The male-to-female ratio for TBI is nearly 2:1, and TBI is much more common in persons younger than 35 years.

Pathophysiology

Appropriate management of TBI requires an understanding of the pathophysiology of head injury. In addition to the obvious functional differences, the brain has several features that distinguish it from other organ systems. The most important of these differences is that the brain is contained within the skull, a rigid and inelastic container. Because the brain is housed within this inelastic container, only small increases in volume within the intracranial compartment

can be tolerated before pressure within the compartment rises dramatically. This concept is defined by the Monro-Kellie doctrine, which states that the total intracranial volume is fixed because of the inelastic nature of the skull. The intracranial volume (Vi/c) is equal to the sum of its components, as follows:

Vi/c = V (brain) + V (cerebrospinal fluid) + V (blood)

In the typical adult, the intracranial volume is approximately 1500 mL, of which the brain accounts for 85-90%, intravascular cerebral blood volume accounts for 10%, and cerebrospinal fluid (CSF) accounts for the remainder (<3%). When a significant head injury occurs, cerebral edema often develops, which increases the relative volume of the brain. Because the intracranial volume is fixed, the pressure within this compartment rises unless some compensatory action occurs, such as a decrease in the volume of one of the other intracranial components. This is intimately related to the concept of intracranial compliance, which is defined as the change in pressure due to changes in volume.

Compliance = Change in volume / change in pressure

Compliance is based on the pressure volume index (PVI) within the intracranial compartment. The PVI describes the change in intracranial pressure (ICP) that occurs when a small amount of fluid is added to or withdrawn from the intracranial compartment. Simply stated, the brain has very limited compliance and cannot tolerate significant increases in volume that can result from diffuse cerebral edema or from significant mass lesions such as a hematoma. The rationale for each treatment of head injury is based on the concept of the Monro-Kellie doctrine and how a particular intervention affects the intracranial compliance. When the volume of any of the components of the total intracranial volume is decreased, the ICP may be decreased.

A second crucial concept in TBI pathophysiology is the concept of cerebral perfusion pressure (CPP). CPP is defined as the difference between the mean arterial pressure (MAP) and the ICP.

CPP = MAP - ICP

In practical terms, CPP is the net pressure of blood delivery to the brain. In the noninjured brain in individuals without long-standing hypertension, cerebral blood flow (CBF) is constant in the range of MAPs of 50-150 mm Hg. This is due to autoregulation by the arterioles, which will constrict or dilate within a specific range of blood pressure to maintain a constant amount of blood flow to the brain.

When the MAP is less than 50 mm Hg or greater than 150 mm Hg, the arterioles are unable to autoregulate and blood flow becomes entirely dependent

on the blood pressure, a situation defined as pressure-passive flow. The CBF is no longer constant but is dependent on and proportional to the CPP. Thus, when the MAP falls below 50 mm Hg, the brain is at risk of ischemia due to insufficient blood flow, while a MAP greater than 160 mm Hg causes excess CBF that may result in increased ICP. While autoregulation works well in the noninjured brain, it is impaired in the injured brain. As a result, pressure-passive flow occurs within and around injured areas and, perhaps, globally in the injured brain.

TBI may be divided into 2 categories, primary brain injury and secondary brain injury. Primary brain injury is defined as the initial injury to the brain as a direct result of the trauma. This is the initial structural injury caused by the impact on the brain, and, like other forms of neural injury, patients recover poorly. Secondary brain injury is defined as any subsequent injury to the brain after the initial insult. Secondary brain injury can result from systemic hypotension, hypoxia, elevated ICP, or as the biochemical result of a series of physiologic changes initiated by the original trauma. The treatment of head injury is directed at either preventing or minimizing secondary brain injury.

Elevated ICP may result from the initial brain trauma or from secondary injury to the brain. In adults, normal ICP is considered 0-15 mm Hg. In young children, the upper limit of normal ICP is lower, and this limit may be considered 10 mm Hg. Elevations in ICP are deleterious because they can result in decreased CPP and decreased CBF, which, if severe enough, may result in cerebral ischemia. Severe elevations of ICP are dangerous because, in addition to creating a significant risk for ischemia, uncontrolled ICP may cause herniation. Herniation involves the movement of the brain across fixed dural structures, resulting in irreversible and often fatal cerebral injury.

CLINICAL PRESENTATION

TBI may be divided into 2 broad categories, closed head injury and penetrating head injury. This is not purely a mechanistic division because some aspects of the treatment of these 2 types of TBIs differ. The clinical presentation of the patient with TBI varies significantly, from an ambulatory patient complaining of a sports-related head injury to the moribund patient arriving via helicopter following a high-speed motor vehicle accident. The Glasgow Coma Scale (GCS) developed by Jennett and Teasdale is used to describe the general level of consciousness of patients with TBI and to define broad categories of head injury. The GCS is divided into 3 categories, eye opening (E), motor response (M), and verbal response (V). The score is determined by the sum of the score in each of the 3 categories, with a maximum score of 15 and a minimum score of 3, as follows: GCS score = E + M + V.

Patients who are intubated are unable to speak, and their verbal score cannot be assessed. They are evaluated only with eye opening and motor scores,

and the suffix T is added to the score to indicate that the patient is intubated. In intubated patients, the maximal GCS score is 10T and the minimum score is 2T. The GCS is often used to help define the severity of TBI. Mild head injuries are generally defined as those associated with a GCS score of 13-15, and moderate head injuries are those associated with a GCS score of 9-12. A GCS score of 8 or less defines a severe head injury. These definitions are not rigid and should be considered as a general guide to the level of injury.

Relevant Anatomy

Several aspects of neuroanatomy and neurophysiology require review in a discussion of TBI. Although a comprehensive review of neuroanatomy is beyond the scope of this discussion, a few key concepts are reviewed.

The brain essentially floats within the CSF; as a result, the brain can undergo significant translation and deformation when the head is subjected to significant forces. In a deceleration injury, in which the head impacts a stationary object such as the windshield of a car, the skull stops moving almost instantly. However, the brain continues to move within the skull toward the direction of the impact for a very brief period after the head has stopped moving. This results in significant forces acting on the brain as it undergoes both translation and deformation.

In an acceleration injury, as in a direct blow to the head, the force applied to the skull causes the skull to move away from the applied force. The brain does not move with the skull, and the skull impacts the brain, causing translation and deformation of the brain. The forces that result from either deceleration or acceleration of the brain can cause injury by direct mechanical effects on the various cellular components of the brain or by shear-type forces on axons. In addition to the translational forces, the brain can experience significant rotational forces, which can also lead to shear injuries.

The intracranial compartment is divided into 3 compartments by 2 major dural structures, the falx cerebri and the tentorium cerebelli. The tentorium cerebelli divides the posterior fossa or infratentorial compartment (the cerebellum and the brainstem) from the supratentorial compartment (cerebral hemispheres). The falx cerebri divides the supratentorial compartment into 2 halves and separates the left and right hemispheres of the brain. Both the falx and the tentorium have central openings and prominent edges at the borders of each of these openings. When a significant increase in ICP occurs, caused by either a large mass lesion or significant cerebral edema, the brain can slide through these openings within the falx or the tentorium, a phenomenon known as herniation. As the brain slides over the free dural edges of the tentorium or the falx, it is frequently injured by the dural edge.

Several types of herniation exist, as follows: (1) transtentorial herniation, (2) subfalcine herniation, (3) central herniation, (4) upward herniation, and (5)

tonsillar herniation. Transtentorial herniation occurs when the medial aspect of the temporal lobe (uncus) migrates across the free edge of the tentorium. This causes pressure on the third cranial nerve, interrupting parasympathetic input to the eye and resulting in a dilated pupil. This unilateral dilated pupil is the classic sign of transtentorial herniation and usually (80%) occurs ipsilateral to the side of the transtentorial herniation. In addition to pressure on the third cranial nerve, transtentorial herniation compresses the brainstem.

Subfalcine herniation occurs when the cingulate gyrus on the medial aspect of the frontal lobe is displaced across the midline under the free edge of the falx. This may compromise the blood flow through the anterior cerebral artery complexes, which are located on the medial side of each frontal lobe. Subfalcine herniation does not cause the same brainstem effects as those caused by transtentorial herniation.

Central herniation occurs when a diffuse increase in ICP occurs and each of the cerebral hemispheres is displaced through the tentorium, resulting in significant pressure on the upper brainstem.

Upward, or cerebellar, herniation occurs when either a large mass or increased pressure in the posterior fossa is present and the cerebellum is displaced in an upward direction through the tentorial opening. This also causes significant upper brainstem compression.

Tonsillar herniation occurs when increased pressure develops in the posterior fossa. In this form of herniation, the cerebellar tonsils are displaced in a downward direction through the foramen magnum, causing compression on the lower brainstem and upper cervical spinal cord as they pass through the foramen magnum.

Another aspect of the intracranial anatomy that has a significant role in TBI is the irregular surface of the skull underlying the frontal and temporal lobes. These surfaces contain numerous ridges that can cause injury to the inferior aspect of the frontal lobes and the temporal lobes as the brain glides over these irregular ridges following impact. Typically, these ridges cause cerebral contusions. The roof of the orbit has many ridges, and, as a result, the inferior frontal lobe is one of the most common sites of traumatic cerebral contusions.

INVESTIGATIVE STUDIES

Lab Studies

After the patient has been stabilized and an appropriate neurologic examination has been conducted, the diagnostic evaluation may begin. Patients with TBI do not require any additional blood tests beyond the standard panel of tests obtained in all trauma patients. A urine toxicology screen and an assessment of the blood alcohol level are important for any patient who has an altered level of

consciousness because any central nervous system depressant can impair consciousness.

Imaging Studies

Skull radiographs. Once an important part of the head injury evaluation, skull radiographs have been replaced by CT scans and are rarely used in patients with closed head injury. Skull radiographs are occasionally used in the evaluation of penetrating head trauma, and they can help provide a rapid assessment of the degree of foreign body penetration in nonmissile penetrating head injuries (eg, stab wounds). Skull radiographs are sometimes used in patients with gunshot wounds to the head to screen for retained intracranial bullet fragments.

CT scan. A CT scan is the diagnostic study of choice in the evaluation of TBI because it has a rapid acquisition time, is universally available, is easy to interpret, and is reliable. When first introduced more than 25 years ago, CT scans of the brain required almost 30 minutes to complete. This acquisition time has decreased steadily; the current generation of ultrafast CT scanners can perform a head CT scan in less than 1 minute, faster than the time required to enter patient's demographic data into the scanner.

The standard CT scan for the evaluation of acute head injury is a noncontrast scan that spans from the base of the occiput to the top of the vertex in 5-mm increments. Three data sets are obtained from the primary scan, (1) bone windows, (2) tissue windows, and (3) subdural windows. These different types of exposure are necessary because of the significant difference in exposure necessary to visualize various intracranial structures. The bone windows allow for a detailed survey of the bony anatomy of the skull, and the tissue windows allow for a detailed survey of the brain and its contents. The subdural windows provide better visualization of intracranial hemorrhage, especially those hemorrhages adjacent to the brain (eg, subdural hematomas).

Each intracranial structure has a characteristic density, which is expressed in Hounsfield units. These units are defined according to a scale that ranges from (-) 1000 units to (+) 1000 units. Air is assigned a density of (-) 1000 units, water is assigned a density of 0 units, and bone has a density of (+) 1000 units. On this scale, CSF has a density of (+) 4 to (+) 10 units, white matter has a density of (+) 22 to (+) 36 units, and gray matter has a density of (+) 32 to (+) 46 units. Extravascular blood has a density of (+) 50 to (+) 90 units, and calcified tissue and bone have a density of (+) 800 to (+) 1000 units.

When reviewing a CT scan, using a systematic approach and following this same protocol each time are important. Consistency is much more important than the specific order used. First, examine the bone windows for fractures, beginning with the cranial vault and then examining the skull base and the facial bones. Next, examine the tissue windows for the presence of (1) extra-axial hematomas (eg, epidural hematomas, subdural hematomas), (2) intraparenchy-

mal hematomas, or (3) contusions. Next, survey the brain for any evidence of pneumocephalus, hydrocephalus, cerebral edema, midline shift, or compression of the subarachnoid cisterns at the base of the brain. Finally, examine the subdural windows for any hemorrhage that may not be visualized easily on the tissue windows.

Skull fractures may be classified as either linear or comminuted fractures. Linear skull fractures are sometimes difficult to visualize on the individual axial images of a CT scan. The scout film of the CT scan, which is the equivalent of a lateral skull x-ray film, often demonstrates linear fractures. The intracranial sutures are easily mistaken for small linear fractures. However, the sutures have characteristic locations in the skull and have a symmetric suture line on the opposite side. Small diploic veins, which traverse the skull, may also be interpreted as fractures. Comminuted fractures are complex fractures with multiple components. Comminuted fractures may be displaced inwardly; this is defined as a depressed skull fracture.

Extra-axial hematomas include epidural and subdural hematomas. Epidural hematomas are located between the inner table of the skull and the dura. They are typically biconvex in shape because their outer border follows the inner table of the skull and their inner border is limited by locations at which the dura is firmly adherent to the skull. Epidural hematomas are usually caused by injury to an artery, although 10% of epidural hematomas may be venous in origin. The most common cause of an epidural hematoma is a linear skull fracture that passes through an arterial channel in the bone. The classic example of this is the temporal epidural hematoma caused by a fracture through the course of the middle meningeal artery. Epidural hematomas, especially those of arterial origin, tend to enlarge rapidly.

Subdural hematomas are located between the dura and the brain. Their outer edge is convex, while their inner border is usually irregularly concave. Subdural hematomas are not limited by the intracranial suture lines; this is an important feature that aids in their differentiation from epidural hematomas. Subdural hematomas are usually venous in origin, although some subdural hematomas are caused by arterial injuries. The classic cause of a posttraumatic subdural hematoma is an injury to one of the bridging veins that travel from the cerebral cortex to the dura. As the brain atrophies over time, the bridging veins become more exposed and, as a result, are more easily injured. Occasionally, the distinction between a subdural and an epidural hematoma can be difficult. The size of an extra-axial hematoma is a more important factor than whether the blood is epidural or subdural in location. In addition, a mixed hematoma with both a subdural and an epidural component is not uncommon.

Intra-axial hematomas are defined as hemorrhages within the brain parenchyma. These hematomas include intraparenchymal hematomas, intraventricular hemorrhages, and subarachnoid hemorrhages. Subarachnoid hemorrhages that occur because of trauma are typically located over gyri on the convexity of the

brain. The subarachnoid hemorrhages that result from a ruptured cerebral aneurysm are usually located in the subarachnoid cisterns at the base of the brain. Cerebral contusions are posttraumatic lesions in the brain that appear as irregular regions, in which high-density changes (ie, blood) and low-density changes (ie, edema) are present. Frequently, 1 of these 2 types of changes predominates within a particular contusion. Contusions are most often caused by the brain gliding over rough surfaces, such as the rough portions of the skull that are present under the frontal and temporal lobes.

CT scans may be used for classification and for diagnostic purposes. Marshall et al published a classification scheme that classifies head injuries according to the changes demonstrated on CT scan images. This system defines 4 categories of injury, from diffuse injury I to diffuse injury IV.

In diffuse injury I, evidence of any significant brain injury is lacking.

In diffuse injury II, either no midline shift or a shift of less than 5 mm is present and the CSF cisterns at the base of the brain are widely patent. In addition, no high-density or mixed-density lesions (contusions) of greater than 25 mL in volume are present.

In diffuse injury III, a midline shift of less than 5 mm is present, with partial compression or absence of the basal cisterns. No high- or mixed-density lesions with a volume greater than 25 mL are present.

Diffuse injury IV is defined as midline shift greater than 5 mm with compression or absence of the basal cisterns and no lesions of high or mixed density greater than 25 mL.

MRI. MRI has a limited role in the evaluation of acute head injury. Although MRI provides extraordinary anatomic detail, it is not commonly used to evaluate acute head injuries because of its long acquisition times and the difficulty in obtaining MRIs in persons who are critically ill. However, MRI is used in the subacute setting to evaluate patients with unexplained neurologic deficits.

MRI is superior to CT scan for helping identify diffuse axonal injury (DAI) and small intraparenchymal contusions. DAI is defined as neuronal injury in the subcortical gray matter or the brainstem as a result of severe rotation or deceleration. DAI is often the reason for a severely depressed level of consciousness in patients who lack evidence of significant injury on CT scan images and have an ICP that is within the reference range. Magnetic resonance angiography may be used in some patients with TBI to assess for arterial injury or venous sinus occlusion.

Angiography. Once a common diagnostic study in persons with acute head injury, angiography is rarely used in the evaluation of acute head injury today. Prior to the development of the CT scan, cerebral angiography provided a reliable means for demonstrating the presence of an intracranial mass lesion. Currently, angiography in used in acute head injury only when a vascular injury may be present. This includes patients with unexplained neurologic deficits, es-

pecially in the setting of temporal bone fractures, and patients with clinical evidence of a potential carotid injury (eg, hemiparesis, Horner syndrome).

Other Tests

Initial evaluation. The initial evaluation of patients with TBI involves a thorough systemic trauma evaluation according to the advanced trauma life support (ATLS) guidelines. Once this has been completed and the patient is stable from a cardiopulmonary standpoint, attention may be directed to a focused head injury evaluation.

The evaluation of the spine for potential injury is critically important in patients with TBI because approximately 10% of those with severe head injuries have a concomitant spine injury. Many of these injuries are cervical spine injuries.

Attempt to obtain a thorough history of the mechanism of the trauma and the events immediately preceding the trauma. Specific information, such as the occurrence of syncope or the onset of a seizure prior to a fall or a motor vehicle accident, prompts a more extended evaluation of the etiology of such an event. Because many patients with TBI have altered levels of consciousness, the history is often provided by family members, police officers, paramedics, or witnesses.

Neurologic assessment

After sufficient information has been obtained regarding patient history, appropriate physical and neurologic examinations are performed. The neurologic assessment begins with ascertaining the GCS score. This is a screening examination and does not substitute for a thorough neurologic examination. In addition to determining the GCS score, the neurologic assessment of patients with TBI should include the following:

- Brainstem examination - Pupillary examination, ocular movement examination, corneal reflex, gag reflex
- Motor examination
- Sensory examination
- Reflex examination

Many patients with TBI have significant alterations of consciousness and/or pharmaceuticals present that limit the scope of the neurologic examination. When such factors limit the neurologic examination, noting their presence is important.

Pupillary examination

A careful pupillary examination is a critical part of the evaluation of patients with TBI, especially in patients with severe injuries. When muscle relaxants have been administered to a patient, the only aspect of the neurologic examination that may be evaluated is the pupillary examination.

Several factors can alter the pupillary examination results. Narcotics cause pupillary constriction (meiosis), and medications or drugs that have sympathomimetic properties cause pupillary dilation (mydriasis). These effects are often strong enough to blunt or practically eliminate pupillary responses. Prior eye surgery, such as cataract surgery, can also alter or eliminate pupillary reactivity.

Proper assessment of the pupillary response requires the use of a strong light source to override any of the potential factors that may affect pupillary reaction. Each pupil must be assessed individually, with at least 10 seconds between assessment of each eye to allow consensual responses to fade prior to stimulating the opposite eye.

A normal pupillary examination result consists of bilaterally reactive pupils that react to both direct and consensual stimuli. Bilateral small pupils can be caused by narcotics, pontine injury (due to disruption of sympathetic centers in the pons), or early central herniation (mass effect on the pons).

Bilateral fixed and dilated pupils are secondary to inadequate cerebral perfusion. This can result from diffuse cerebral hypoxia or severe elevations of ICP preventing adequate blood flow into the brain.

Pupils that are fixed and dilated usually indicate an irreversible injury. If due to systemic hypoxia, the pupils sometimes recover reactivity when adequate oxygenation is restored.

A unilateral fixed (unresponsive) and dilated pupil has many potential causes. A pupil that does not constrict when light is directed at the pupil but constricts when light is directed into the contralateral pupil (intact consensual response) is indicative of a traumatic optic nerve injury.

A unilateral dilated pupil that does not respond to either direct or consensual stimulation usually indicates transtentorial herniation.

Unilateral constriction of a pupil is usually secondary to Horner syndrome, in which the sympathetic input to the eye is disrupted and the pupil constricts due to more parasympathetic than sympathetic stimulation. In patients with TBI, Horner syndrome may be caused by an injury to the sympathetic chain at the apex of the lung or a carotid artery injury. A unilateral constricted pupil can be caused by a unilateral brainstem injury, but this is quite rare.

A core optic pupil is a pupil that appears irregular in shape. This is caused by a lack of coordination of contraction of the muscle fibers of the iris and is associated with midbrain injuries.

Ocular movement examination

When the patient's level of consciousness is altered significantly, a loss of voluntary eye movements often occurs and abnormalities in ocular movements are frequently present. These abnormalities can provide specific clues to the extent and location of injury.

Ocular movements involve the coordination of multiple centers in the brain, including the frontal eye fields, the paramedian pontine reticular formation (PPRF), the medial longitudinal fasciculus (MLF), and the nuclei of the

third and sixth cranial nerves. In patients in whom voluntary eye movements cannot be assessed, oculocephalic and oculovestibular testing may be performed.

Oculocephalic testing

Oculocephalic testing (doll's eyes) involves observation of eye movements when the head is turned from side to side. This maneuver helps assess the integrity of the horizontal gaze centers.

Before performing oculocephalic testing, the status of the cervical spine must be established. If a cervical spine injury has not been excluded reliably, oculocephalic testing should not be performed. When assessing oculocephalic movements, the head is elevated to 30° from horizontal and is rotated briskly from side to side. A normal response is for the eyes to turn away from the direction of the movement as if they are fixating on a target that is straight ahead. This is similar to the way a doll's eyes move when the head is turned; this is the origin of the term doll's eyes. If the eyes remain fixed in position and do not rotate with the head, this is indicative of dysfunction in the lateral gaze centers and is referred to as negative doll's eyes. Some patients may have negative doll's eyes and normal oculovestibular reflexes.

Oculovestibular testing

Oculovestibular testing, also known as cold calorics, is another method for assessment of the integrity of the gaze centers. Oculovestibular testing is performed with the head elevated to 30° from horizontal to bring the horizontal semicircular canal into the vertical position.

Oculovestibular testing requires the presence of an intact tympanic membrane; this must be assessed before beginning the test. In oculovestibular testing, 20 mL of ice-cold water is instilled slowly into the auditory canal. If is no response occurs within 60 seconds, the test is repeated with 40 mL of cold water. When cold water is irrigated into the external auditory canal, the temperature of the endolymph falls and the fluid begins to settle. This causes an imbalance in the vestibular signals and initiates a compensatory response.

Cold-water irrigation in the ear of an alert patient results in a fast nystagmus away from the irrigated ear and a slow compensatory nystagmus toward the irrigated side. If warm water is used, the opposite will occur; the fast component of nystagmus will be toward the irrigated side, and the slow component will be away from the irrigated side. This is the basis for the acronym COWS, which stands for cold opposite, warm same. This refers to the direction of the fast component of nystagmus. As the level of consciousness declines, the fast component of nystagmus fades gradually. Thus, in unconscious patients, only the slow phase of nystagmus may be evaluated. A normal oculocephalic response to cold-water calorics (ie, eye deviation toward the side of irrigation) indicates that the injury spares the PPRF, the MLF, and third and sixth cranial nerve nuclei. This means that the level of injury must be rostral to the reticular activating system in the upper brainstem. If a unilateral frontal lobe injury is present, the eyes

are deviated toward the side of injury prior to caloric testing. Cold-water irrigation of the opposite ear results in a normal response to caloric testing (ie, eye deviation toward the irrigated side) because the injury is in the frontal region and spares the pontine gaze centers. When a pontine injury is present, the eyes often deviate away from the side of injury. In this situation, cold-water irrigation of the contralateral ear does not cause the gaze to deviate toward the irrigated ear because an injury has occurred at the level of the pons and the pontine gaze centers are compromised. A dysconjugate response to caloric testing suggests an injury to either the third or sixth cranial nerves or an injury to the MLF, resulting in an internuclear ophthalmoplegia. If caloric testing causes a skew deviation, in which the eyes are dysconjugate in the vertical direction, this indicates a lesion in the brainstem. The exact location of injury that results in skew deviation is not known.

Motor examination

After completing the brainstem examination, a motor examination should be performed. A thorough motor or sensory examination is difficult to perform in any patient with an altered level of consciousness. When a patient is not alert enough to cooperate with strength testing, the motor examination is limited to an assessment of asymmetry in the motor examination findings. This may be demonstrated by an asymmetric response to central pain stimulation or a difference in muscle tone between the left and right sides. A finding of significant asymmetry during the motor examination may be indicative of a hemispheric injury and raises the possibility of a mass lesion.

Sensory examination

Performing a useful sensory examination in patients with TBI is often difficult. Patients with altered levels of consciousness are unable to cooperate with sensory testing, and findings from a sensory examination are not reliable in patients who are intoxicated or comatose.

Peripheral reflex examination

A peripheral reflex examination can be useful to help identify gross asymmetry in the neurologic examination. This may indicate the presence of a hemispheric mass lesion.

TREATMENT

Medical therapy: The treatment of head injury may be divided into the treatment of closed head injury and the treatment of penetrating head injury. While significant overlap exists between the treatments of these 2 types of injury, some important differences are discussed. Closed head injury treatment is divided further into the treatment of mild, moderate, and severe head injuries.

Closed head injury

Mild head injury

Most head injuries are mild head injuries. Most people presenting with mild head injuries will not have any progression of their head injury; however, up to 3% of mild head injuries progress to more serious injuries. Mild head injuries may be separated into low-risk and moderate-risk groups. Patients with mild-to-moderate headaches, dizziness, and nausea are considered to have low-risk injuries. Many of these patients require only minimal observation after they are assessed carefully, and many do not require radiographic evaluation. These patients may be discharged if a reliable individual can monitor them.

Patients who are discharged after mild head injury should be given an instruction sheet for head injury care. The sheet should explain that the person with the head injury should be awakened every 2 hours and assessed neurologically. Caregivers should be instructed to seek medical attention if patients develop severe headaches, persistent nausea and vomiting, seizures, confusion or unusual behavior, or watery discharge from either the nose or the ear.

Patients with mild head injuries typically have concussions. A concussion is defined as physiologic injury to the brain without any evidence of structural alteration. Concussions are graded on a scale of I-V. A grade I concussion is one in which a person is confused temporarily but does not display any memory changes. In a grade II concussion, brief disorientation and anterograde amnesia of less than 5 minutes' duration are present. In a grade III concussion, retrograde amnesia and loss of consciousness for less than 5 minutes are present, in addition to the 2 criteria for a grade II concussion. Grade IV and grade V concussions are similar to a grade III, except that in a grade IV concussion, the duration of loss of consciousness is 5-10 minutes, and in a grade V concussion, the loss of consciousness is longer than 10 minutes.

As many as 30% of patients who experience a concussion develop post-concussive syndrome (PCS). PCS consists of a persistence of any combination of the following after a head injury: headache, nausea, emesis, memory loss, dizziness, diplopia, blurred vision, emotional lability, or sleep disturbances. Fixed neurologic deficits are not part of PCS, and any patient with a fixed deficit requires careful evaluation. PCS usually lasts 2-4 months. Typically, the symptoms peak 4-6 weeks following the injury. On occasion, the symptoms of PCS last for a year or longer. Approximately 20% of adults with PCS will not have returned to full-time work 1 year after the initial injury, and some are disabled permanently by PCS. PCS tends to be more severe in children than in adults. When PCS is severe or persistent, a multidisciplinary approach to treatment may be necessary. This includes social services, mental health services, occupational therapy, and pharmaceutical therapy.

After a mild head injury, those displaying persistent emesis, severe headache, anterograde amnesia, loss of consciousness, or signs of intoxication by drugs or alcohol are considered to have a moderate-risk head injury. These patients should be evaluated with a head CT scan. Patients with moderate-risk mild head injuries can be discharged if their CT scan findings reveal no pathology, their intoxication is cleared, and they have been observed for at least 8 hours.

Moderate and severe head injury

The treatment of moderate and severe head injuries begins with initial cardiopulmonary stabilization by ATLS guidelines. The initial resuscitation of a patient with a head injury is of critical importance to prevent hypoxia and hypotension. In the Traumatic Coma Data Bank study, patients with head injury who presented to the hospital with hypotension had twice the mortality rate of patients who did not present with hypotension. The combination of hypoxia and hypotension resulted in a mortality rate 2.5 times greater than if neither of these factors was present.

Once a patient has been stabilized from the cardiopulmonary standpoint, evaluation of their neurologic status may begin. The initial GCS score provides a classification system for patients with head injuries but does not substitute for a neurologic examination. After assessment of the coma score, a neurologic examination should be performed. If a patient has received muscle relaxants, the only neurologic response that may be evaluated is the pupillary response.

After a thorough neurologic assessment has been performed, a CT scan of the head is obtained. The results of the CT scan help determine the next step. If a surgical lesion is present, arrangements are made for immediate transport to the operating room. Fewer than 10% of patients with TBI have an initial surgical lesion.

Although no strict guidelines exist for defining surgical lesions in persons with head injury, most neurosurgeons consider any of the following to represent indications for surgery in patients with head injuries: extra-axial hematoma with midline shift greater than 5 mm, intra-axial hematoma with volume greater than 30 mL, an open skull fracture, or a depressed skull fracture with more than 1 cm of inward displacement. In addition, any temporal or cerebellar hematoma that is larger than 3 cm in diameter is considered a high-risk hematoma because these regions of the brain are smaller and do not tolerate additional mass as well as the frontal, parietal, and occipital lobes. These high-risk temporal and cerebellar hematomas are usually evacuated immediately

If no surgical lesion is present on the CT scan image, or following surgery if one is present, treatment of the head injury begins. The first phase of treatment is to institute general measures. Once appropriate fluid resuscitation has been completed and the volume status is determined to be normal, intravenous fluids

are administered to maintain the patient in a state of euvolemia or mild hypervolemia. A previous tenet of head injury treatment was fluid restriction, which was believed to limit the development of cerebral edema and increased ICP. Fluid restriction decreases intravascular volume and, therefore, decreases cardiac output. A decrease in cardiac output often results in decreased cerebral flow, which results in decreased brain perfusion and may cause an increase in cerebral edema and ICP. Thus, fluid restriction is contraindicated in patients with TBI.

Another supportive measure used to treat patients with head injuries is elevation of the head. When the head of the bed is elevated to 20-30°, the venous outflow from the brain is improved, thus helping to reduce ICP. If a patient is hypovolemic, elevation of the head may cause a drop in cardiac output and CBF; therefore, the head of the bed is not elevated in hypovolemic patients. In addition, the head should not be elevated (1) in patients in whom a spine injury is a possibility or (2) until an unstable spine has been stabilized.

Sedation is often necessary in patients with traumatic injury. Some patients with moderate head injuries have significant agitation and require sedation. In addition, patients with multisystem trauma often have painful systemic injuries that require pain medication, and many intubated patients require sedation. Short-acting sedatives and analgesics should be used to accomplish proper sedation without eliminating the ability to perform periodic neurologic assessments. This requires careful titration of medication doses and periodic weaning or withholding of sedation to allow periodic neurologic assessment.

The use of anticonvulsants in patients with TBI is a controversial issue. No evidence exists that the use of anticonvulsants decreases the incidence of late-onset seizures in patients with either closed head injury or TBI. Temkin et al demonstrated that the routine use of Dilantin in the first week following TBI decreases the incidence of early-onset (within 7 d of injury) seizures but does not change the incidence of late-onset seizures. In addition, the prevention of early posttraumatic seizures does not improve the outcome following TBI. Therefore, the prophylactic use of anticonvulsants is not recommended for more than 7 days following TBI and is considered optional in the first week following TBI.

After instituting general supportive measures, the issue of ICP monitoring is addressed. ICP monitoring has consistently been shown to improve outcome in patients with head injuries. ICP monitoring is indicated for any patient with a GCS score less than 9, any patient with a head injury who requires prolonged deep sedation or pharmacologic relaxants for a systemic condition, or any patient with an acute head injury who is undergoing extended general anesthesia for a nonneurosurgical procedure.

ICP monitoring involves placement of an invasive probe to measure the ICP. Unfortunately, noninvasive means of monitoring ICP do not exist, although they are under development. ICP may be monitored by means of an intraparenchymal monitor, an intraventricular monitor (ventriculostomy), or an epidural

monitor. These devices measure ICP by fluid manometry, strain-gauge technology, or fiberoptic technology.

Intraparenchymal ICP monitors are devices that are placed into the brain parenchyma to measure ICP by means of fiberoptic, strain-gauge, or other technologies. The intraparenchymal monitors are very accurate; however, they do not allow for drainage of CSF. Epidural devices measure ICP via a strain-gauge device placed through the skull into the epidural space. This is an older form of ICP measurement and is rarely used today because the other technologies available are more accurate and more reliable.

A ventriculostomy is a catheter placed through a small twist drill hole into the lateral ventricle. The ICP is measured by transducing the pressure in a fluid column. Ventriculostomies allow for drainage of CSF, which can be effective in decreasing the ICP.

Once an ICP monitor has been placed, ICP is monitored continuously. No absolute value of ICP exists for which treatment is implemented automatically. In adults, the reference range of ICP is 0-15 mm Hg. The normal ICP waveform is a triphasic wave, in which the first peak is the largest peak and the second and third peaks are progressively smaller. When intracranial compliance is abnormal, the second and third peaks are usually larger than the first peak. In addition, when intracranial compliance is abnormal and ICP is elevated, pathologic waves may appear.

Lundberg described 3 types of abnormal ICP waves, A, B, and C waves. Lundberg A waves, known as plateau waves, have a duration of 5-20 minutes and an amplitude of 50 mm Hg over the baseline ICP. After an episode of A waves dissipates, the ICP is reset to a baseline level that is higher than when the waves began. Lundberg A waves are a sign of severely compromised intracranial compliance. The rapid increase in ICP caused by these waves can result in a significant decrease in CPP and may lead to herniation.

Lundberg B waves have a duration of less than 2 minutes, and they have an amplitude of 10-20 mm Hg above the baseline ICP. B waves are also related to abnormal intracranial compliance. Because of their smaller amplitude and shorter duration, B waves are not as deleterious as A waves.

C waves, known as Hering-Traube waves, are low-amplitude waves that may be superimposed on other waves. They may be related to increased ICP; however, C waves can also occur in the setting of normal ICP and compliance.

When treating elevated ICP, remember that the goal of treatment is to optimize conditions within the brain to prevent secondary injury and to allow the brain to recover from the initial insult. Maintaining ICP within the reference range is part of an approach designed to optimize both CBF and the metabolic state of the brain. Treatment of elevated ICP is a complex process that should be tailored to each particular patient's situation and should not be approached in a "cookbook" manner. Many potential interventions are used to lower ICP, and

each of these is designed to improve intracranial compliance, which results in improved CBF and decreased ICP.

The Monro-Kellie doctrine provides the framework for understanding and organizing the various treatments for elevated ICP. In patients with head injuries, the total intracranial volume is composed of the total volume of the brain, the CSF, intravascular blood volume, and any intracranial mass lesions. The volume of one of these components must be reduced to improve intracranial compliance and to decrease ICP. The discussion of the different treatments for elevated ICP is organized according to which component of intracranial volume they affect.

The first component of total intracranial volume to consider is the blood component. This includes all intravascular blood, both venous and arterial, and comprises approximately 10% of total intracranial volume. Elevation of the head increases venous outflow and decreases the volume of venous blood within the brain. This results in a small improvement in intracranial compliance and, therefore, has only a modest effect on ICP.

The second component of intracranial vascular volume is the arterial blood volume. This may be reduced by mild-to-moderate hyperventilation, in which the PCO_2 is reduced to 30-35 mm Hg. This decrease in PCO_2 causes vasoconstriction at the level of the arteriole, which decreases blood volume enough to reduce ICP. The effects of hyperventilation have a duration of action of approximately 48-72 hours, at which point the brain resets to the reduced level of PCO_2. This is an important point because once hyperventilation is used, the PCO_2 should not be returned to normal rapidly. This may cause rebound vasodilatation, which can result in increased ICP.

At one time, severe hyperventilation was an important component of the treatment of increased ICP. Reducing PCO_2 to less than 25 mm Hg has been shown to cause enough vasoconstriction that CBF is reduced to the point at which a high probability exists of developing cerebral ischemia. Therefore, prolonged severe hyperventilation is not used routinely to treat elevated ICP. Brief periods of severe hyperventilation may be used to treat patients with transient ICP elevations due to pressure waves or in the initial treatment of patients in neurologic distress until other measures can be instituted.

CSF represents the next component of total intracranial volume and accounts for 2-3% of total intracranial volume. In adults, total CSF production is approximately 20 mL/h or 500 mL/d. In many patients with TBI who have elevated ICP, a ventriculostomy may be placed and CSF may be drained. Removal of small amounts of CSF hourly can result in improvements in compliance that result in significant improvements in ICP.

The third and largest component of total intracranial volume is the brain or tissue component, which comprises 85-90% of the total intracranial volume. When significant brain edema is present, it causes an increase in the tissue component of the total intracranial volume and results in decreased compliance and

increased ICP. Treatments for elevated ICP that reduce total brain volume include diuretics, perfusion augmentation (CPP strategies), metabolic suppression, and decompressive procedures.

Diuretics are powerful in their ability to decrease brain volume and, therefore, decrease ICP. Mannitol, an osmotic diuretic, is the most common diuretic used. Mannitol is a sugar alcohol that draws water out from the brain into the intravascular compartment. It has a rapid onset of action and a duration of action of 2-8 hours. Mannitol is usually administered as a bolus because it is much more effective when given in intermittent boluses than when used as a continuous infusion. The standard dose ranges from 0.25-1 g/kg, administered every 4-6 hours. Because mannitol causes significant diuresis, electrolytes and serum osmolality must be monitored carefully during its use. In addition, careful attention must be given to providing sufficient hydration to maintain euvolemia. The limit for mannitol is 4 g/kg/d. At daily doses higher than this, mannitol can cause renal toxicity. Mannitol should not be given if the patient's serum sodium level is greater than 145 or serum osmolality is greater than 315 mOsm.

Other diuretics that sometimes are used in patients with TBI include furosemide, glycerol, and urea. Mannitol is preferred over furosemide because it tends to cause less severe electrolyte imbalances than a loop diuretic. Interestingly, mannitol and furosemide have a synergistic effect when combined; however, this combination tends to cause severe electrolyte disturbances. Urea and glycerol have also been used as osmotic diuretics. Both of these compounds are smaller molecules than mannitol and, as a result, tend to equilibrate within the brain sooner than mannitol; therefore, they have a shorter duration of action than mannitol. Urea has the additional problem that it can cause severe skin sloughing if it infiltrates into the skin.

CPP management involves artificially elevating the blood pressure to increase the MAP and the CPP. Because autoregulation is impaired in the injured brain, pressure-passive CBF develops within these injured areas. As a result, these injured areas of the brain often have insufficient blood flow, and tissue acidosis and lactate accumulation occur. This causes vasodilation, which increases cerebral edema and ICP. When the CPP is raised to greater than 65-70 mm Hg, the ICP is often lowered because increased blood flow to injured areas of the brain decreases the tissue acidosis. This often results in a significant decrease in ICP.

Metabolic therapies are designed to decrease the cerebral metabolic rate, which decreases ICP. Metabolic therapies are powerful means of reducing ICP, but they are reserved for situations in which other therapies have failed to control ICP. This is because metabolic therapies have diffuse systemic effects and often result in severe adverse effects, including hypotension, immunosuppression, coagulopathies, arrhythmias, and myocardial suppression. Metabolic suppression may be achieved through drug therapies or induced hypothermia.

Barbiturates are the most common class of drugs used to suppress cerebral metabolism. Barbiturate coma is typically induced with pentobarbital. A loading dose of 10 mg/kg is administered over 30 minutes, and then 5 mg/kg/h is administered for 3 hours. A maintenance infusion of 1-2 mg/kg/h is begun after loading is completed. The infusion is titrated to provide burst suppression on continuous electroencephalogram monitoring and a serum level of 3-4 mg/dL. Typically, the barbiturate infusion is continued for 48 hours, and then the patient is weaned off the barbiturates. If the ICP again escapes control, the patient may be reloaded with pentobarbital and weaned again in several days.

Hypothermia may also be used to suppress cerebral metabolism. The use of mild hypothermia involves decreasing the core temperature to 34-35°C for 24-48 hours and then slowly rewarming the patient over 2-3 days. Patients with hypothermia are also at risk for hypotension and systemic infections.

Another treatment that may be used in patients with TBI with refractory ICP elevation is decompressive craniectomy. In this surgical procedure, a large section of the skull is removed and the dura is expanded. This increases the total intracranial volume and, therefore, decreases ICP. Which patients benefit from decompressive craniectomy has not been established. Some believe that patients with refractory ICP elevation who have diffuse injury but do not have significant contusions or infarctions will benefit from decompressive craniectomy.

Management of elevated ICP involves using a combination of treatments. Each patient represents a slightly different set of circumstances, and treatment must be tailored to each patient. Although no rigid protocols have been established for the treatment of head injury, many published algorithms provide treatment schemas.

The American Association of Neurologic Surgeons published a comprehensive evidence-based review of the treatment of TBI, called the "Guidelines for the Management of Severe Head Injury." In these guidelines, 3 different categories of treatments, standards, guidelines, and options are outlined. Standards are the accepted principles of management that reflect a high degree of clinical certainty. Guidelines are a particular strategy or a range of management options that reflect a high degree of clinical certainty. Options are strategies for patient management for which clinical certainty is unclear.

Penetrating trauma

The treatment of penetrating brain injuries involves 2 main aspects. The first is the treatment of the TBI caused by a penetrating object. Penetrating brain injuries, especially from high-velocity missiles, frequently result in severe ICP elevations. This aspect of penetrating brain injury treatment is identical to the treatment of closed head injuries.

The second aspect of penetrating head injury treatment involves debridement and removal of the penetrating objects. Penetrating injuries require careful

debridement because these wounds are frequently dirty. When objects penetrate the brain, they introduce pathogens into the brain from the scalp surface and from the surface of the penetrating object.

Penetrating injuries may be caused by high-velocity missiles (eg, bullets), penetrating objects (eg, knives, tools), or fragments of bone driven into the brain. Bullet wounds are treated with debridement of as much of the bullet tract as possible, dural closure, and reconstruction of the skull as needed. If the bullet can be removed without significant risk of neurologic injury, it should be removed to decrease the risk of subsequent infection. Penetrating objects such as knives require removal to prevent further injury and infection. If the penetrating object either is near or traverses a major vascular structure, an angiogram is necessary to assess for potential vascular injury. When the risk of vascular injury is present, penetrating objects should be removed only after appropriate access has been obtained to ensure that vascular control is easily achieved.

Penetrating brain injuries are associated with a high rate of infection, both early infections and delayed abscesses. Appropriate debridement and irrigation of wounds helps to decrease the infection rate. Some of the risk factors for infection following penetrating brain injury include extensive bony destruction, persistent CSF leak, and an injury pathway that violates an air sinus.

Late-onset epilepsy is a common consequence of penetrating brain injuries and can occur in up to 50% of patients with penetrating brain injuries. No evidence exists that prophylactic anticonvulsants decrease the development of late-onset epilepsy. During the Vietnam War, prophylactic anticonvulsants were used, and the rate of late-onset epilepsy was not different from that of previous wars, when prophylactic anticonvulsants were not used.

HEAD INJURY IN CHILDREN

Head injuries in children differ from head injuries in adults in several ways. Children tend to have more diffuse injuries than adults, and traumatic intracerebral hematomas are less common in children than in adults. In addition, early posttraumatic seizures are more common in children than in adults. Overall, children have much lower morbidity and mortality rates from traumatic head injury compared to adults.

When a child with a head injury is being evaluated, nonaccidental trauma must be excluded. In the United States, as many as 1 million cases of nonaccidental trauma in children may occur annually. TBI is the most common cause of morbidity and mortality in nonaccidental trauma in children.

Radiographic signs of nonaccidental trauma include unexplained multiple or bilateral skull fractures, subdural hematomas of different ages, cortical contusions and shearing injures, cerebral ischemia, and retinal hemorrhages. If any of these are present, the case should be referred to the proper child welfare agency.

COMPLICATIONS

Complications resulting from TBI are common and can be divided into 2 categories, systemic and neurologic complications. The systemic complications of TBI are typical of any severe injury and depend on the types of intensive treatments used. Be aware of the complications of intensive care treatment when considering systemic complications of head injury. The neurologic complications of TBI include focal neurologic deficits, global neurologic deficits, seizures, CSF fistulae, hydrocephalus, vascular injuries, infections, and brain death.

Focal neurologic deficits

Focal neurologic deficits are quite common following TBI. Cranial nerves are affected often because of their anatomic location at the base of the brain. When the brain shifts within the skull as it undergoes either acceleration or deceleration forces, significant force is often placed on the entire brain and the cranial nerves. The cranial nerves are tethered at their exit sites from the skull, and, as a result, they may be stretched when the brain shifts as a result of acceleration or deceleration forces. In addition, the cranial nerves are very susceptible to injury as they course through narrow bony canals and grooves. The cranial nerves that are injured most commonly in patients with TBI are cranial nerves I, IV, VII, and VIII.

Anosmia caused by traumatic injury to the first cranial nerve occurs in 2-38% of patients with TBI. It is more common in those with frontal fractures and in those with posttraumatic rhinorrhea. Posttraumatic anosmia improves slowly, and as many as one third of patients do not show any improvement in olfaction.

Injuries to the fourth cranial nerve, the trochlear nerve, are also quite common. This nerve is often injured in patients with head trauma because it has the longest intracranial course of the cranial nerves. Injury to the trochlear nerve causes a positional diplopia, in which those affected experience diplopia when they look down and toward the eye in which the trochlear nerve is injured. As a result, to compensate, the head is tilted up and away from the side of the injury. Trochlear nerve injuries resolve fully in approximately two thirds of those with unilateral injury and in one fourth of those with bilateral injuries.

Facial nerve injuries often occur with head injuries in which the temporal bone is fractured. From 10-30% of persons with longitudinal fractures of the temporal bone and 30-50% of those with transverse fractures of the temporal bone have either acute or delayed facial nerve injury. Immediate facial nerve injury suggests direct injury to the nerve, while delayed injury suggests progressive edema within the nerve. In severely injured patients, a delay in the diagnosis of facial nerve injuries occurs frequently because facial nerve function is difficult to assess in obtunded patients.

Cochlear nerve injury (cranial nerve VIII) is also a common occurrence in patients with head injury, especially in patients with temporal bone fractures. In addition, vestibular disorders, including vertigo, dizziness, and tinnitus, are extremely common in patients with head injuries.

Hydrocephalus

Hydrocephalus is a common late complication of TBI. Posttraumatic hydrocephalus may present as either ventriculomegaly with increased ICP or as normal pressure hydrocephalus. In patients with increased ICP secondary to posttraumatic hydrocephalus, the typical signs of hydrocephalus are often observed and include headaches, visual disturbances, nausea/vomiting, and alterations in the level of consciousness. Normal pressure hydrocephalus usually manifests as memory problems, gait ataxia, and urinary incontinence.

The diagnosis of normal pressure hydrocephalus may be difficult to make in patients with TBI because they often have memory difficulties and gait abnormalities secondary to their head injury. In addition, as many as 86% of patients with TBI demonstrate some degree of ventriculomegaly on follow-up CT scan images. This ventriculomegaly is often secondary to diffuse brain atrophy, and radiographic features rarely help make the distinction between atrophy and normal pressure hydrocephalus. Any patient who develops neurologic deterioration weeks to months following TBI should be evaluated for the possibility of normal pressure hydrocephalus. When CT scan findings cannot help distinguish between normal pressure hydrocephalus and ventriculomegaly secondary to brain atrophy, a high-volume lumbar puncture tap test is performed to ascertain if CSF drainage would improve the patient's neurologic condition.

Seizures

Posttraumatic seizures are a frequent complication of TBI and are divided into 3 categories. Early seizures occur within 24 hours of the initial injury, intermediate seizures occur 1-7 days following injury, and late seizures occur more than 7 days after the initial injury. Posttraumatic seizures are very common in those with a penetrating cerebral injury, and late seizures occur in as many as half of these patients.

Cerebrospinal fluid fistulae

Cerebrospinal fistulae, either in the form of rhinorrhea or otorrhea, may occur in as many as 5-10% of patients with TBI. They may present either immediately or in a delayed fashion and are more frequent in patients with basilar skull fractures. Approximately 80% of acute cases of CSF rhinorrhea resolve spontaneously within 1 week. A 17% risk of meningitis exists when CSF rhinorrhea is present. Prophylactic antibiotics have not been demonstrated to decrease this meningitis risk, although very few studies have examined this issue. More

than 95% of acute episodes of CSF otorrhea resolve spontaneously within 1 week, and CSF otorrhea is complicated by meningitis in fewer than 4% of cases.

When acute CSF fistulae do not resolve spontaneously, a lumbar subarachnoid drain may be placed for several days in an attempt to divert CSF and allow the fistula to close. If this fails, radiographic dye is introduced into the subarachnoid space via lumbar puncture (metrizamide cisternogram), and a high-resolution CT scan is performed in an attempt to identify the origin of the CSF fistula. A craniotomy is performed, and the fistula site is repaired. Delayed CSF fistulae may occur from 1 week after the initial injury to years later. These delayed fistulae are more difficult to treat and frequently require surgical intervention.

Vascular injuries

Vascular injuries are uncommon sequelae of TBIs. Arterial injuries that may occur following head trauma include arterial transactions, thromboembolic phenomena, posttraumatic aneurysms, dissections, and carotid-cavernous fistulae (CCF).

Arterial occlusions secondary to transactions or thromboembolism following closed head injuries are uncommon occurrences.

Posttraumatic intracranial aneurysms, which are also rare, differ from congenital aneurysms because the posttraumatic aneurysms tend to be located distally, as opposed to the congenital aneurysms, which are typically proximal in location.

Arterial dissections are more common than the aforementioned arterial injuries and should be considered if significant injury has occurred to the petrous portion of the temporal bone, through which the carotid artery passes, or when an unexplained neurologic deficit is present. A cerebral angiogram is often necessary to help exclude arterial injury in these cases.

Posttraumatic CCF occur when the internal carotid artery is injured within the cavernous sinus, resulting in a direct connection between the carotid artery and the veins of the cavernous sinus. This overloads the venous system and results in chemosis and proptosis on the affected side. Other signs of CCF include diplopia, ophthalmoplegia, visual disturbances, and headaches. Some high-risk fistulae may cause intracerebral hemorrhage. CCF are treated with endovascular balloon occlusion of the fistula origin.

Specific intracranial venous injuries are uncommon following TBI if one excludes the injury to the bridging veins, which are the most common source of subdural hematomas. Depressed skull fractures overlying any of the major intracranial venous sinuses may cause injury to the sinus. When these venous sinus injuries require treatment, substantial, and sometimes life-threatening, blood loss can occur.

A second type of venous injury following TBI involves venous sinus thrombosis. Although very rare following head injury, this is a potentially life-

threatening injury because the impaired venous drainage often causes severe ICP elevations and venous infarction. The treatment for venous sinus thrombosis is anticoagulation, which presents significant risk in those with acute head injuries. If the thrombosis progresses despite systemic anticoagulation, direct intracranial intravenous thrombolysis is necessary.

Infections

Intracranial infections are another potential complication of TBI. In uncomplicated closed head injury, infection is uncommon. When basilar skull fractures and/or CSF fistulae are present, the risk of infection is increased. In addition, if a patient has had a ventriculostomy for ICP monitoring, the risk of infection is also increased, for either a ventriculitis or meningitis. Other intracranial infections such as subdural or epidural empyema and intraparenchymal abscesses are rare following closed head injury. As one would expect, the incidence of infection in penetrating cerebral injuries and open depressed skull fractures increases.

Brain death

Brain death can result from either massive initial injury or as the result of prolonged severe elevations of ICP. Brain death is defined as the absence of brain function. A rigid protocol is necessary to prove that brain death has occurred. It must be established that no sedating medications or neuromuscular blocking agents are present. The patient's electrolyte levels, blood count, body temperature, and arterial blood gas values must be within the reference ranges. The neurologic examination should demonstrate fixed nonreactive pupils, lack of corneal and gag reflexes, fixed position of the eyes during rotation of the head (ie, negative doll's eyes), no response to supraorbital pain, and no movement of the eyes to cold-water calorics.

A lack of any neurologic response is not sufficient to establish brain death, and confirmatory testing must be performed. One of these tests is an apnea test, which involves removing a patient from the ventilator for a brief period to assess any sign of spontaneous respiration. This is performed after a 30-minute preoxygenation period with 100% oxygen. At the conclusion of the testing period, if the patient has not had any spontaneous respirations and the arterial blood gas measurements demonstrate a PCO_2 of greater than 65 mm Hg, the test results are consistent with brain death. Two neurologic examinations and 2 apnea tests 12 hours apart are sufficient for determining brain death. A nuclear blood flow study or a cerebral angiogram may be performed instead of one of the apnea tests for brain death determination. The results of these studies demonstrate the absence of CBF when brain death has occurred. In most states, brain death is considered to be death.

OUTCOME AND PROGNOSIS

The outcome of TBI is related to the initial level of injury. While the initial GCS score provides a description of the initial neurologic condition, it does not correlate tightly with outcome. Various methods have been used in an attempt to predict the outcome of TBI, and these are beyond the scope of this discussion. However, one simplified model uses 3 factors, ie, age, motor score of the GCS, and pupillary response (ie, normal, unilateral unresponsive pupil, bilateral unresponsive pupils), to provide a probability of outcome.

The Traumatic Coma Data Bank analyzed 780 patients with head injuries and identified 5 factors that correlated with a poor outcome, as follows: (1) age older than 60 years, (2) initial GCS score of less than 5, (3) presence of a fixed dilated pupil, (4) prolonged hypotension or hypoxia early after injury, and (5) presence of a surgical intracranial mass lesion.

Many methods exist for evaluating the outcome of TBI. A simple and commonly used method is the Glasgow outcome scale. This divides outcome into 5 categories, as follows: (1) good, (2) moderate disability, (3) severe disability, (4) vegetative, and (5) dead. The scale can be divided further into good outcomes (eg, good plus moderate disability) and poor outcomes (eg, severe disability, vegetative, dead).

Future and controversies

The treatment of TBI has undergone significant change in the last 20 years. A tremendous national effort has been undertaken to promote head injury prevention. Mandatory air bags in automobiles and the helmet laws have significantly reduced the incidence of serious head injuries.

The future of head injury treatment has several major goals. One of these goals is to develop a noninvasive ICP monitor. Transcranial low-frequency ultrasound has shown promise as a potential noninvasive ICP monitor; however, it has not undergone clinical testing. Significant efforts have been directed toward the development of a noninvasive CBF monitor. Cerebral oxygen monitoring as an adjunct to ICP monitoring is under active investigation. The need also exists for a more effective treatment to control ICP that is refractory to standard therapies.

The most significant controversy today in the treatment of TBI is the minimum desirable CPP to achieve in the patient with a head injury. Previously, a CPP of 79 mm Hg was considered the minimum; however, many now believe that a CPP of 60 mm Hg is sufficient. Further controversy also exists as to whether elevated ICP or decreased CPP is a more important prognostic factor. This is an important distinction because it directs the main goals of therapy in severely injured patients. If ICP elevations are considered a more important fac-

tor, then efforts may be directed at lowering ICP as a primary goal and improving CPP as a secondary goal. If one considers CPP to be the more important factor, then the primary goal of treatment should be to maintain an appropriate CPP.

BRAIN TUMORS

Approximately 20,000 primary central nervous system (CNS) tumors are diagnosed each year in the United States. These tumors tend to affect younger patients and are the second most frequent cause of cancer-related death among children, the third most frequent cause of cancer-related death among patients 15 to 35 years of age, and the fourth most frequent cause of cancer-related death among patients 36 to 45 years of age. However, the incidence of the histologically more malignant tumors seems to be rising, especially among the elderly.

Primary CNS tumors are thought to arise from precursor cells to nervous system elements. In tumor cells, an accumulation of aberrant genetic events allows dysregulation of differentiation and growth; the result is neoplastic proliferation. This proliferation results in the development of a mass, which becomes clinically apparent with neurologic symptoms. This chapter discusses some of the more frequent tumors, including glioma (astrocytoma, anaplastic astrocytoma, glioblastoma, and oligodendroglioma), primitive neuroectodermal tumor (medulloblastoma), ependymoma, and meningioma. Also discussed is primary CNS lymphoma, which is being seen with increasing frequency in the immunocompromised and immunocompetent population.

CLINICAL FEATURES AND IMAGING DIAGNOSIS

From a clinical and imaging viewpoint, brain tumours are most easily divided by site and relationship to the cranial fossae:

1. extracranial but involving neural tissue (e.g. head and neck lesions)
2. intracranial but extracerebral
   - anterior cranial fossa (olfactory groove)
   - middle cranial fossa (pituitary region and sphenoid wing)
   - posterior cranial fossa (cerebello-pontine angle, craniocervical junction)
3. within the brain substance (primary or secondary intracerebral tumours)

Head and neck lesions

Patients with tumours of the head and neck most commonly present with headache, lower cranial neuropathies, or facial pain. Where the involvement is in the nasopharynx one should consider nasopharyngeal carcinoma, adenoid cystic carcinoma, and metastatic tumours. Where there is involvement of the carotid body region, glomus jugulare should be considered. Patients with glomus jugu-

lare tumours commonly present with lower cranial nerve palsies, e.g. dysphonia, dysphagia with wasted tongue or weak palate, but, if extensive, it can also cause pulsatile tinnitus, headaches, and hearing loss. Glomus jugulare tumours are usually large when eventually discovered. Plain radiographs (submento-vertex view) will best demonstrate the enlargement of the jugular foramen. CT scanning shows the strongly enhancing tumour mass with erosion of the adjacent bone. MRI will demonstrate the 'salt and pepper' appearance caused by the flow voids within the tumour. Gadolinium-enhanced coronal MRI scan is particularly useful to delineate the extent of the tumour and the relationship to the brainstem. Where there is occipital headache, and lower cranial neuropathies, tumour involvement of the skull base should be considered. In the midline, chordoma, chondroma, and chondrosarcoma are all possible. Imaging of the head/neck by CT scan or MRI scan may demonstrate a lesion with or without soft-tissue involvement. CT scanning is superior when bony involvement is present (e.g. skull osteomas, Paget's disease, fibrous dysplasia) and MRI, with its multiplanar capabilities, is superior for soft-tissue visualization (e.g. nasopharyngeal carcinoma, metastases, and glomus jugulare tumours). Contrast enhancement will better delineate blood vessels from surrounding soft-tissue structures, and ENT opinion, angiography, and simple blood tests (e.g. alkaline phosphatase and myeloma screen) may also be helpful.

Intracranial extracerebral lesions

Anterior cranial fossa

Patients with olfactory groove meningiomas usually present late when the tumour is large enough to cause headache, seizures, or personality changes. Anosmia is rarely complained of in the absence of other symptoms, being usually unilateral.

Middle cranial fossa including pituitary region

Pituitary tumours may present because of endocrine effects (hormone excess or hypopituitarism) or mass effect. Women with prolactinomas commonly present with amenorrhoea and galactorrhoea and are referred to gynaecologists. Men with prolactinomas usually present later than women and may complain of headache, reduced sexual function, and visual field defects. The presence of acromegaly or steroid excess will point to a diagnosis of a growth-hormone- or ACTH-secreting macroadenoma, respectively, and should stimulate a request for imaging of the pituitary region. Plain lateral skull radiographs may show a 'double floor' or erosion of the sella tursica in the presence of a pituitary macroadenoma. Skull radiography, however, may be entirely normal in macroadenoma and is always normal in microadenomas, and is insufficient to exclude any intracranial tumour. Investigations for hormone-secreting pituitary tumour include prolactin levels, growth hormone levels, and serum or urinary cortisols, plus im-

aging of the pituitary gland by multiplanar, contrast-enhanced MRI, or contrast-enhanced coronal CT with fine cuts through the pituitary gland.

Craniopharyngiomas commonly present with symptoms and signs of mild hypopituitarism or diabetes insipidus. Almost 90 per cent of men complain of impotence, while most women complain of amenorrhoea. Children present with short stature, and 40 per cent of patients will be hypothyroid at presentation while 25 per cent have adrenal insufficiency. Fifty per cent of patients will have diabetes insipidus and headache. Craniopharyngiomas are usually a complex combination of cysts and solid tumour with calcification. There is generally no surrounding oedema in the brain. Craniopharyngiomas can be difficult to differentiate from dermoid or epidermoid tumours or Rathke's pouch cysts but they generally have more complex cysts than epidermoids, thicker irregular walls, and more calcification on CT scan. Hypopituitarism is also found in 20 per cent of patients with epidermoid and dermoid cysts in the suprasellar or parasellar areas.

Patients with visual-field loss due to optic nerve or chiasm compression and will be referred to ophthalmologists, physicians, or neurologists. The visual impairment may be due to pathology in the nerve (e.g. glioma), or pressure on the nerve from a tumour (pituitary tumour, craniopharyngioma, meningioma, metastasis) or cyst (dermoid, epidermoid, Rathke's pouch cyst). Symptoms will lead to imaging of the anterior visual pathway. Multiplanar gadolinium-enhanced MRI imaging is the investigation of choice. The coronal images will provide useful information about expansion of the optic nerves consistent with an optic nerve glioma or meningioma, and about the parasellar region and the relationship with any extrinsic pressure on the optic chiasm. Pituitary macroadenomas usually cause expansion of the pituitary fossa and displace the optic chiasm upwards, producing a bitemporal field loss which starts in the superior temporal quadrants. The visual field defects with pituitary macroadenomas will vary, depending on whether the optic chiasm is prefixed or postfixed. Craniopharyngiomas expand downwards from the hypothalamus and cause a bitemporal hemianopia, most frequently involving the inferior temporal quadrants, but can also cause a variety of visual field defects, depending on where the tumour presses on the visual apparatus. Epidermoid and dermoid cyst generally appear on CT scanning as well-circumscribed lesions with low density, between that of CSF and brain, due to cholesterol or keratin granules. The wall of epidermoid cysts may be thinly calcified, and since the contents are avascular they do not enhance with contrast. Dermoids are more heterogeneous, have a thicker wall, rarely enhance, and more commonly demonstrate calcification. There is generally no surrounding oedema in the brain. On T1-weighted MRI sequences, epidermoids exhibit a variable signal (white when the lipid content is high or black if the lipid content is low). Classically, epidermoids have low signal on T1-weighted images and very high signal on T2-weighted images. Dermoids give high signal on T1-weighted images in areas containing fat and variable signal

where there is a combination of fat, muscle, and bone, and they may be mistaken for a craniopharyngioma or mixed germ cell tumour (teratoma). Mixed germ cell tumours are more heterogeneous than germ cell tumours (germinomas) because they contain a variety of tissues, including bone, cartilage, hair, and fatty tissue. Enhancement following contrast is common in germ cell tumours. Tumours such as hypothalamic astrocytomas and oligodendrogliomas can also extend downwards to cause chiasmal or optic nerve compression and hypopituitarism. These tumours are usually solid with areas of calcification but can also sometimes be exophytic. Rathke's cleft cysts are simple intrasellar cysts containing CSF. Meningiomas are usually easily differentiated from cysts and other tumours; however, en plaque meningioma of the optic nerve may be difficult to visualize, even with gadolinium-enhanced MRI, and should always be considered as a potential diagnosis in patients with progressive optic nerve disease even in the absence of a clear mass lesion on MRI.

Patients who present with periorbital pain, ocular muscle paralysis, or ptosis may have tumours in the orbit (e.g. metastases, lymphoma, lacrimal gland carcinoma) or tumours of the sphenoid wing (e.g. meningioma, carcinoma, dermoid, epidermoid or large pituitary tumours, or craniopharyngioma). Differential diagnosis will depend on the speed of onset of symptoms and the imaging appearance.

Posterior fossa

If the presenting complaint is facial numbness or weakness, or deafness, tinnitus or vertigo, patients are likely to be sent by their family practitioners to see a physician or ENT surgeon. The differential diagnosis includes acoustic neuroma, meningioma, haemangioblastoma, meningioma, dermoid, epidermoid,lipoma, and metastasis.

The most common tumour of the cerebellopontine angle is an acoustic neuroma. Patients most commonly present with deafness, tinnitus, or vertigo. Patients with meningiomas less commonly have acoustic nerve symptoms and more commonly present with other cranial nerve involvement (especially facial numbness and facial weakness); however, differentiating on clinical grounds is unreliable. MRI is the most sensitive imaging technique to delineate lesions of the middle or posterior cranial fossae. Acoustic neuromas usually expand the acoustic nerve and may cause expansion of the internal auditory meatus. Small tumours enhance I uniformly and are usually easy to distinguish from other tumours; however, if acoustic neuromas are very large, it may be difficult to identify the origin of the tumour and distinguish it from a meningioma. Meningiomas strongly enhance uniformly on CT, reflecting the vascularity of these tumours, but necrosis, cysts, and calcification can alter the signal characteristics on MRI, making differentiation from dermoids or even haemangioblastomas rather difficult. Cholesteatomas and epidermoids can commonly be differenti-

ated from meningiomas and acoustic neuromas by their relative lack of enhancement.

If the lower cranial nerves are involved, it is imperative to get good imaging of the base of the skull, neural exit foramina, and extracranial soft tissues in the neck.

Intracerebral lesions

Headache, memory or personality changes, and seizures are the most common initial symptoms in patients with primary intracerebral tumours; however, patients are commonly referred to hospital only when focal symptoms or signs become obvious (e.g. seizures, hemiparesis papilloedema, dysphasia, or hemianopia). Hemiparesis or hemisensory loss are the most common symptoms.

Nearly all patients who have weakness or numbness complain of these symptoms, thus directing the clinician to the abnormality on examination. Only 7 per cent of patients with malignant glioma complain of visual symptoms, yet over 20 per cent have signs of visual field loss and 23 per cent have papilloedema, therefore, careful examination of the visual fields and fundi is important in anyone complaining of headaches or symptoms suggestive of disturbance of higher mental function. Most commonly the upper motor neuron weakness is mild initially and affects fine manipulation first and mild progressive lower limb weakness (hip flexion, knee flexion, and ankle dorsiflexion). Clinical follow-up using quick, sensitive, simple tests such as the timed nine-hole peg test, timed 10 m walk, and a test of memory and grading of dysphasia are usually sufficient to assess clinical response to treatment. The Barthel Activities of Daily Living Index may be a useful measure in elderly patients or in patients with metastases where the weakness is commonly severe, but it is insensitive, and its 'ceiling effect' precludes its use in trials of glioma in general and it does not record cognitive disability or dysphasia. The Karnofsky Performance Scale is useful for grading patients for entry into studies, but in practice a three-point grading scale (>60, 60-50, <50) rather than an 11-point scale (100, 90, 80 ... 10, 0) is usually used. It can be used to follow individual patients, although intra-observer and inter-observer errors limit its usefulness.

Stroke-like onset or collapse with coma, occurs in about 5 per cent of patients with intracerebral tumours and is most commonly related to haemorrhage into a malignant brain tumour (malignant glioma or metastasis). Stroke-like presentations and subacute presentations with cognitive deficits, visualfield disorders, or dysphasia are more common in the elderly, and most commonly suggest a poor prognosis. Late-onset epilepsy (first seizure after age 18) is a common presentation in patients who have low-grade gliomas and meningiomas. It has been estimated that between 3 and 10 per cent of patients with late-onset epilepsy have an underlying tumour of some form. Seizures are the first presenting symptom in 54 per cent of low-grade gliomas, 50 per cent of anaplastic as-

trocytomas, 26 per cent of meningiomas, 19 per cent of glioblastomas, 15 per cent of metastases, and 11 per cent of primary CNS lymphomas. Over a follow-up period of 3 years, the prevalence of seizures rises to 70 per cent in low-grade glioma, 56 per cent in anaplastic astrocytoma, 48 per cent in glioblastoma, 44 per cent in meningioma, 39 per cent in primary CNS lymphoma, and 31 per cent in metastases. Tumour-associated epilepsy is partial (focal) in approximately 50 per cent of patients, partial epilepsy with secondary generalization in 25 per cent, and tonic-clonic seizures without warning in 25 per cent of patients. Children are more likely to have posterior fossa, or deep thalamic region tumours and present with cerebellar symptoms or, more frequently, symptoms of raised intracranial pressure.

CT and MRI brain scanning have improved the management of patients with brain tumours dramatically, but diagnostic interpretation is not without its difficulties. The addition of MRI spectroscopy may increase the specificity of diagnostic imaging, although this requires further prospective study. The three levels of diagnosis are: 1. Is it a tumour?; 2. What type of tumour is it?; 3. If it is a glioma, what grade of glioma is it?

Is it a tumour?

Neuroradiologists will correctly predict an intracerebral tumour in about 90-95 per cent of cases. However, approximately 10 per cent of patients will have had a previous CT or MRI scan that has been reported as either normal or an alternative pathology. In these cases, MRI will usually demonstrate an abnormality but the aetiology of the lesion may not be clear. Even in the best centres 5-10 per cent of CT scans reported by a radiologist as being an intracerebral tumour will later be found to have non-malignant pathologies. The differential diagnosis of non-contrast-enhancing lesions, with standard doses of contrast, include demyelination, encephalitis, infarct, post-traumatic, and non-specific changes. The differential diagnosis in patients with contrast-enhancing lesions includes demyelination, arteriovenous malformation, haemorrhagic stroke, and cerebral abscess. In some cases who present with a stroke-like onset, it may not be evident that the haemorrhage has occurred into an existing mass lesion. The common tumours to present with intratumoural haemorrhage are glioblastoma, metastatic lung cancer, melanoma, and choriocarcinoma.

What type of tumour is it?

Errors in reporting of CT or MRI are even more common when attempts are made to predict the type of malignancy. The main areas of difficulty are where tumours have an exophytic extension with involvement of the meninges, intense contrast enhancement, or sometimes calcification of meningeal/vascular origin (e.g. meningioma/haemangiopericytoma) or of glial origin (e.g. glioblastoma or oligodendroglioma). In these cases it may be very difficult to say

whether the tumour is extracerebral and invading the brain, or intrinsic and becoming exophytic.

It has been estimated that 5 per cent of brain images reported as multiple metastases by experienced neuroradiologists will actually turn out to be primary brain tumours (glioma or primary CNS lymphoma). In one study of single brain metastasis, 11 per cent of patients with known systemic malignancy with a solitary brain lesion thought on imaging to be a metastasis turned out to have a different pathology (in some cases the pathology was not a tumour at all). Primary CNS lymphoma can be unifocal (60 per cent) or multifocal (40 per cent). Cells are densely packed and generally homogeneously enhance and thus are commonly mistaken for metastases.

I. Glioma is the most common intracranial tumor, comprising about 60% of all primary CNS neoplasms. Although there are several grading systems currently in use, the three-tiered classification system has become the most popular. Astrocytoma is the most well-differentiated and lowest-grade tumor. Anaplastic astrocytoma is an intermediate-grade tumor, and glioblastoma is the most malignant and poorly differentiated glioma. The most malignant form, glioblastoma, is the most common, representing 50% to 60% of cases of glioma diagnosed. Most studies of all grades of glioma show either no sex preponderance or a slight male bias. These tumors do not tend to be inherited, except in a few rare syndromes (e.g., neurofibromatosis, Li-Fraumeni syndrome, tuberous sclerosis, and ataxia-telangiectasia). No definite environmental association of these tumors has been found in comparisons of urban and rural populations.

A. Astrocytoma

1. Course of disease. Approximately 30% of cases of glioma diagnosed are astrocytoma. This low-grade neoplasm tends to occur among younger patients, typically in the fourth decade of life or earlier. There is a paucity of prospective information regarding the course of astrocytoma. Retrospective analysis has shown age to be an important predictive factor; younger patients, especially those younger than 20 years, have the highest 5-year survival rate. The incidence of malignant transformation and response to therapy are not well known. Total surgical resection and good postoperative performance status have been associated retrospectively with prolonged survival. One exception to the lack of information on low-grade tumors is pilocytic astrocytoma, which occurs most often in children and occasionally in adults. With only surgical intervention, these tumors have an excellent prognosis and only rarely transform to malignant neoplasms. Other tumors that fit into the rubric of low-grade astrocytoma include ganglioglioma and neurocytoma. These tumors tend to behave in a benign manner and to require only surgical intervention.

2. Therapy. Except as noted, no prospective studies have evaluated the efficacy of therapeutic intervention in low-grade astrocytoma. It is accepted that surgical excision is a reasonable initial approach to these tumors, although any further therapy is based only on anecdotal or retrospective analyses. Currently there are no generally accepted guidelines for radiation therapy for low-grade astrocytoma, although many clinicians believe that for some older patients, treatment with high-dose radiation (6,000 cGy) is appropriate. At least initially, chemotherapy is not believed to playa part in treatment of these patients because of the slow growth of these tumors. However, many astrocytomas progress to higher-grade neoplasms, in which case therapy is referable to the more malignant tumor. Follow-up computed tomography (CT) or magnetic resonance imaging (MRI) typically is performed every 6 months and when the patient has clinical changes.

3. Prognosis. Patients with astrocytoma who have the best prognosis are young, have undergone gross total tumor resection, and have minimal or no postoperative neurologic or other deficits. Among these patients, the 5-year survival rate is greater than 80%. Further specific prognostic assessment in other patient subgroups is difficult, but at least a fraction of astrocytomas in such patients progress to higher-grade neoplasms that necessitate other types of therapy. For any patient with a diagnosis of astrocytoma (with the exception of pilocytic astrocytoma, ganglioglioma, and neurocytoma), continual follow-up evaluation is necessary, because malignant transformation can occur at any time.

B. Anaplastic astrocytoma

1. Course of disease. Anaplastic astrocytoma is diagnosed much less frequently than are its lower- and higher-grade counterparts. Part of the reason for this revolves around the pathologic criteria for anaplastic astrocytoma compared with those for glioblastoma (anaplasia without necrosis in the specimen). Even with these criteria, there may still be an overestimation of the incidence of anaplastic astrocytoma because of sampling errors that occur when specimens from subtotal resection or stereotactic biopsy are sent to pathologists for review. It has been estimated that as many as 30% of tumors diagnosed as anaplastic astrocytoma at stereotactic biopsy are of higher grade (glioblastoma). Apart from difficulties with histologic grading, few prospective analyses of these tumors have been performed. Retrospective studies have shown anaplastic astrocytoma to occur typically in the fifth decade of life, usually with a long (more than 1 year) history of neurologic symptoms. The most important favorable prognostic factors include young age and good performance status. Surgery has not been found to influence survival, perhaps because anaplastic tumors tend to be diffusely infiltrating. A high percentage of these tumors recur at higher pathologic grade.

2. Therapy. Patients with anaplastic astrocytoma need a multidisciplinary approach similar to that used for glioblastoma.

a. Surgery and corticosteroids. Surgery should be considered if the diagnosis is in question, if there would be benefit from cytoreduction (reduction of mass effect), or if surgery is indicated because of emergency clinical conditions. Surgery does not seem to affect survival per se. Corticosteroids may be necessary to decrease symptoms of increased intracranial pressure. Dexamethasone often is given at a starting dosage of 4 mg four times a day, titrated for relief of symptoms. Doses greater than 32 mg/d are rarely useful. Minimizing doses of corticosteroids because of known side effects should be an important goal after radiation treatment.

b. Radiation therapy is an important aspect of management of anaplastic astrocytoma, with a current recommended dose of approximately 6,000 cGy. The fractionation schedule of radiation therapy usually ranges from 180 to 200 cGy/d. Focal radiation of 4,500 cGy within a 3-cm margin with a boost of 1,500 cGy for the 1.5-cm margin surrounding the area of enhancement of the tumor has been found as effective as whole-brain irradiation. Highly focused radiation, such as stereotactic radiosurgery may be of palliative benefit at recurrence.

c. Chemotherapy. Anaplastic astrocytoma is managed with both adjuvant and recurrent chemotherapy. Adjuvant chemotherapy (given within 2 weeks after the completion of radiation) usually consists of a combined regimen of procarbazine (60 mg/m2 by mouth on days 8 to 21), lomustine (CCNU; 110 mg/m2 by mouth on day 1), and vincristine (PCV; 1.4 mg/m2 intravenously [i. v.] on days 8 and 29) every 6 to 8 weeks for 1 year or until tumor recurrence. At recurrence, high-dose intravenous carmustine (BCND; 250 mg/m2) is administered every 6 to 8 weeks until further tumor progression. Administration of these drugs requires that specific laboratory values and clinical cautions be assessed periodically. Further therapy after this point usually revolves around phase I or phase II drugs or other experimental therapies. Consultation with a neurooncologist often is necessary. Follow-up CT or MRI evaluation should be performed 6 weeks after completion of radiation therapy and before each cycle of chemotherapy.

3. Prognosis. With implementation of surgery, radiation therapy, and chemotherapy, patients with anaplastic astrocytoma have a median survival period of more than 3 years. Typical time to first tumor recurrence is approximately 2.5 years, and time to death after progression is 8 months. Patients younger than 40 years have the highest likelihood for response to treatment and prolonged survival. Few patients older than 60 years respond to this multimodal approach to therapy, and patients in this age group have the highest incidence of serious side effects. Clinical judgment and careful consideration of the patient's wishes are necessary before any decision regarding therapeutic intervention, especially chemotherapy.

C. Glioblastoma

1. Course of disease. Glioblastoma is the most frequently diagnosed primary CNS neoplasm. Its course, unlike those of astrocytoma and anaplastic as-

trocytoma, is well defined. This tumor is the most malignant of the gliomas and has a poor prognosis with inexorable progression to death. Patients with glioblastoma usually come to medical attention in the sixth decade of life with a short history (less than 6 months) of neurologic symptoms. The best predictors of survival and response to chemotherapy are the same as those for anaplastic astrocytoma-patient age and performance status. A shorter duration of symptoms before diagnosis has been associated with longer survival periods. Currently it is unclear whether extent of surgery is an important prognostic factor.

2. Therapy for glioblastoma is similar to that for anaplastic astrocytoma. Maximal surgical debulking usually is suggested for patients who can undergo the procedure safely. Subsequent high-dose radiation therapy (6,000 cGy or more) is as described for anaplastic tumors. Adjuvant chemotherapy with carmustine usually is initiated within 2 weeks after completion of radiation treatment and is given every 6 to 8 weeks. Recurrence is managed with procarbazine, CCNU, and vincristine, high-dose oral procarbazine alone (each cycle consisting of 150 mg/m^2/day for 28 days, followed by a 28-day rest), or experimental therapy. Consultation with a neurooncologist is necessary at this point. CT or MRI should be performed before each cycle of chemotherapy.

3. The prognosis for patients with glioblastoma is poor. Patients treated with surgery alone have a median survival time of 14 to 26 weeks. The addition of radiation therapy increases the survival period to 40 weeks. Administration of chemotherapy with nitrosoureas such as procarbazine and carmustine further increases the median survival time to 50 weeks and increases the proportion of patients surviving 18 months. Nevertheless, with multimodality therapy, the median survival time is less than 1 year and fewer than 15% of patients survive 2 years.

D. Oligodendroglioma

1. Course of disease. Oligodendroglioma arises from presumed oligodendroglial precursors and usually manifests in the fourth or fifth decade of life. These tumors occur in proportion to the volume of white matter, and hence the frontal lobes are the areas most frequently affected. There is an inconsistent relation between histologic grade and malignant behavior. Few data are available regarding the frequency of malignant degeneration, although it is well known that some oligodendrogliomas transform into glioblastomas. Better prognostic factors include relatively benign histologic features, postoperative radiation therapy, complete surgical resection, and good preoperative and postoperative performance status. Close follow-up care is necessary in the treatment of these patients, especially given the long-term survival of particular subsets.

2. Therapy. Management of the different types of oligodendroglioma is evolving. Maximal surgical excision is considered the initial step in management of these tumors. Radiation therapy can follow surgery in a manner similar to that of anaplastic astrocytoma or glioblastoma. Although there is no strict relation between histologic anaplasia and malignant potential, most neuro-

oncologists suggest that patients with anaplastic oligodendroglioma be treated with multiagent chemotherapy, that is, procarbazine, CCNU, and vincristine. Patients with nonanaplastic oligodendroglioma typically are observed without further therapy after radiation therapy and are given multiagent chemotherapy only at recurrence. For the first year, MRI or CT should be performed before administration of chemotherapy and every 6 to 8 weeks for anaplastic tumors or every 3 months for nonanaplastic oligodendroglioma. Ifthere is no evidence of recurrence, imaging can be performed every 6 months thereafter.

3. The prognosis for oligodendroglioma is more favorable than that for either anaplastic astrocytoma or glioblastoma. Overall, the median survival period is more than 5 years, and the 10-year survival rate is 24%. Selected patients with the particularly good prognostic factors have the likelihood of longer survival.

II. Primitive neuroectodermal tumor (PNET)

A. Course of disease. PNETs are primarily neoplasms of children. These tumors constitute the most frequently diagnosed soft-tissue malignant tumors in the pediatric ages but account for fewer than 1% of all adult tumors. In adults, the median age at diagnosis is 24 years. The most often diagnosed PNET is medulloblastoma, which typically occurs in the posterior fossa. There is a male-to-female ratio of 2: 1. These tumors are graded according to the Chang criteria (TM system), although there is no influence per se on prognosis. Medulloblastoma can metastasize throughout the craniospinal axis, as well as outside the nervous system, for as long as 10 years after the initial diagnosis. Bone, lymph nodes, lung, pleura, liver, and breast are the most frequent sites of seeding outside the nervous system. Prolonged survival is associated with high-dose posterior fossa radiation accompanied by additional radiation therapy to the entire brain, spinal cord, and coverings as well as with early treatment. There may be improved survival among female patients. The extent of surgery is important in relapse-free, but not overall, survival.

B. Therapy. Maximal surgical resection and radiation are the mainstays of therapy for medulloblastoma. Radiation doses of 5,200 to 5,500 cGy to the posterior fossa and 3,600 cGy to the remaining neuraxis are considered appropriate and have been associated with prolonged progression-free survival, particularly in low-stage disease. Management of recurrent disease typically revolves around chemotherapy, although the most beneficial regimen has yet to be defined. However, most neurooncologists recommend a multidrug protocol with drugs such as the nitrosoureas, a platinum-based compound, and steroids. Consultation is required to determine the most current regimen. Imaging studies should be performed after radiation therapy and before each cycle of chemotherapy. Because recurrences are not uncommon, follow-up evaluation of these patients, including periodic radiographic examinations, should be performed for at least 10 years after completion of therapy.

C. Prognosis. With maximal treatment (radiation being paramount in importance), the 5-year survival rate is 50% to 76%, and the 10-year survival rate is 33% to 60%. Recurrence, when it is found, is typically in the posterior fossa. Some patients with more extensive tumors may benefit from chemotherapy in either an adjuvant or a recurrence setting. Those patients with metastatic lesions, especially outside the nervous system, have a worse prognosis than do those who have solitary recurrences in the posterior fossa.

III. Ependymoma

A. Course of disease. Ependymoma, like PNET, is a tumor of the young and is uncommon in adults. The tumor arises most frequently in the central canal of the spinal cord or the filum terminale as well as in white matter adjacent to a ventricular surface. Like medulloblastoma, ependymoma tends to seed throughout the nervous system, although the likelihood of such seeding is defined by the grade of the tumor. Ependymoma is graded in a variety of ways but can be most conveniently divided into differentiated (low-grade, myxopapillary) and anaplastic (high-grade) ependymoma. Anaplastic tumors are most often associated with neuraxial spread. A particular subtype of ependymoma, ependymoblastoma, has an especially high frequency of seeding. However, the usual area of recurrence for all ependymomas is the primary site, although seeding can accompany local treatment failure in the higher grades. Better prognostic factors include low grade, treatment with surgery with little residual tumor remaining postoperatively, and high-dose radiation therapy.

B. Therapy. Evaluation of the entire nervous system and cerebrospinal fluid for malignant cells often is recommended in the management of ependymoma. Maximal surgical resection and radiation therapy are the necessary initial treatments, because local control of disease is a major predictor of outcome. For low-grade tumors, a dose of 5,400 cGy to the primary tumor is considered standard, with no additional treatment of the rest of the nervous system. For anaplastic tumors, 5,400 cGy is applied to the primary tumor site and 3,500 to 4,000 cGy to the neuraxis. Chemotherapy is given at recurrence, although only anecdotal data on the most beneficial regimen are available. Hence, the chemotherapeutic protocol to be followed for recurrence therapy should be determined in consultation with a neurooncologist to determine the most current regimen. Imaging should be performed after radiation therapy and before each chemotherapeutic intervention. Continual follow-up evaluation is necessary because of the possibility of late recurrence.

C. Prognosis. Patients with ependymoma of low grade treated maximally with surgery, radiation, and chemotherapy have a 5-year survival rate of 60% to 80%. Higher-grade disease has a significantly worse prognosis: 10% to 47% of patients survive for 5 years. As with medulloblastoma, seeding carries a worse prognosis.

IV. Meningioma

A. Course of disease. Meningioma is a common nervous system tumor, constituting approximately 15% of all CNS neoplasms. There is a slight female preponderance. Although the peak age at diagnosis is 45 years, asymptomatic tumors are common in older adults as well. These neoplasms grow slowly and typically are benign in behavior. However, the recurrence rate for totally resected tumors is still 10%. Fifteen percent of meningiomas recur if a dural attachment remains after surgery, and 39% recur if only subtotal resection can be accomplished. These tumors occur most frequently in the parasagittal and falx regions, and can be associated with inherited syndromes (e.g., neurofibromatosis). Malignant meningioma, which is rare, has anaplastic pathologic features and behavior and necessitates continual monitoring and treatment.

B. Therapy. Surgical removal is the therapy of choice for meningioma. Cauterization or embolization has been performed on particularly vascular tumors to ease removal. Radiation and chemotherapy play no role in the management of typical meningioma, although malignant tumors may necessitate these additional interventions. Imaging studies should be performed yearly for at least 3 years and if symptoms develop.

C. The prognosis for meningioma is good. Tumors can recur, however, and recurrence necessitates additional surgery or, for malignant meningioma, radiation therapy and chemotherapy.

V. Primary CNS lymphoma

A. Course of disease. Primary CNS lymphoma (PCNSL) is a rare tumor in the immunocompetent population, comprising less than 2% of all brain tumors and extranodal lymphomas. Pathologically, these tumors are typically non-Hodgkin's B-cell tumors, although T-cell tumors are occasionally found. The incidence of PCNSL has been rising, both in the immunocompetent population and, primarily, because of the increasing population of patients with acquired immunodeficiency syndrome (AIDS). Moreover, other immunocompromised patients such as recipients of renal transplants are acquiring PCNSL with increasing frequency. Other immunodeficiency diseases reported in association with PCNSL include Wiskott-Aldrich syndrome, agammaglobulinemia, and ataxia-telangiectasia. Although concurrent non-Hodgkin's lymphoma at other extranodal sites is uncommon in these patients, staging evaluation of a patient found to have PCNSL should include radiographic imaging (CT or MRI) of the chest, abdomen, and pelvis as well as examination of a bone marrow aspirate. Because PCNSL can occur in ocular and meningeal tissues, slit-lamp and cerebrospinal fluid examinations should be performed. Finally, human immunodeficiency virus testing should be performed on all patients with a diagnosis of PCNSL. Combination chemotherapy and radiation therapy has been found to prolong survival significantly in comparison with surgery and radiation alone.

B. Therapy. Use of biopsy alone to establish the diagnosis of PCNSL is the sole surgical intervention required. No additional benefit is derived from subtotal or total resection of any visualized mass. Radiation therapy can be given either initially after biopsy or at recurrence after adjuvant chemotherapy. The optimal regimen has yet to be defined, but combination therapy with both radiation and chemotherapy has been successful in prolonging median survival to more than 40 months, although in some regimens leukoencephalopathy and cognitive changes have been found. Although treatment of patients AIDS and PCNSL has shown tumor regression, ultimately there has been no increase in overall survival rate among these patients.

In the management of PCNSL, the two most successful regimens have entailed large doses of chemotherapy. In the first, disruption of the blood-brain barrier with mannitol has been used with efficacy. Intravenous cyclophosphamide (15 mglkg) and intraarterial methotrexate (2.5 g) are administered with the disruption, oral leucovorin (20 mg every 6 hours) is given 36 hours after completion of the infusion of methotrexate and continued for 5 days, and procarbazine (100 mg/d by mouth) and dexamethasone (24 mg/d by mouth) are given for 14 days after the disruption. This cycle is repeated every 28 days for 1 year. Radiation therapy is given at relapse. In the second regimen, chemotherapy is combined with radiation therapy as adjuvant treatment. Dexamethasone (16 mg/kg by mouth) is given until an Ommaya reservoir has been placed, and then intravenous administration of methotrexate (1 g/m2) is begun, given on days 1 and 8. Intrathecal methotrexate (12 mg through the Ommaya reservoir) is administered on days 1, 4, 8, 11, 15, and 18 with a dexamethasone taper. Whole-brain radiation (4,000 cGy) with a cone-down boost (1,440 cGy) is then given. Three weeks later, cytarabine (Ara-C; 3 g/m2) is given intravenously for 2 days and repeated 3 weeks later. Both regimens have high response rates; the median survival period is more than 40 months. Imaging (preferably MRI) should be performed before each intervention and every 6 to 8 weeks thereafter.

C. The prognosis for PCNSL is better than that for the malignant glial tumors. With radiation and chemotherapy, the median survival of patients with PCNSL can be expected to be greater than 3.5 years. Although each of the regimens has been associated with limited side effects, some studies of high-dose chemotherapy with radiation for PCNSL have shown both leukoencephalopathy and cognitive changes with treatment. Thus, careful assessment and follow-up evaluation of neurologic status is extremely important. Patients with AIDS respond to such regimens; however, prognosis in that patient population is related to the underlying disease.

VI. Treatment toxicity

A. Radiation toxicity can be conveniently classified according to the time of presentation into acute reactions, early delayed reactions, and late delayed reactions.

1. Acute reactions occur during the course of treatment. They consist of symptoms of increased intracranial pressure or worsening of existing neurologic symptoms. These symptoms usually are mild and transient and are thought to result from radiation-induced edema. Occasionally it is temporarily necessary to administer a corticosteroid or to increase the dose.

2. Early delayed reactions occur several weeks to months after completion of radiation treatment. These reactions may manifest as worsening symptoms or as increasing somnolence and fatigue. It is believed that these symptoms are caused by temporary inhibition of myelin synthesis. Although this syndrome is typically temporary and mild, there have been reports of severe reactions necessitating intensive medical support. Careful consideration is necessary to avoid interpreting an early delayed reaction as a treatment failure without enlargement of tumor mass on images.

3. Late delayed reactions may occur months to years after completion of radiation therapy. The main type of late delayed reaction is radiation necrosis, which can mimic tumor recurrence in that it can be progressive, irreversible, and fatal. Higher doses of external beam radiation, used in treating patients with glioblastoma and with stereotactic radiosurgery, are most frequently associated with radiation necrosis. This effect may be a result of damage to small and medium-sized arterioles or a direct effect on glial cells. Radiation necrosis is difficult to diagnose without biopsy. Use of a variety of anatomic (MRI and CT) and functional (positron emission tomography and single photon emission CT) imaging modalities has not facilitated reliable differentiation of necrosis from tumor recurrence. Management of suspected or confirmed radiation necrosis usually entails surgery; however, only total resection (compared with biopsy) is clinically beneficial. There is anecdotal evidence that anticoagulants (heparin and warfarin) may be useful therapy for radiation necrosis at dosages used in stroke management.

B. Chemotherapy toxicity. All drugs used in the management of glioma can cause myelosuppression, which in the case of the alkylating agents, is typically delayed and cumulative. Because of this, weekly blood counts, measurement of electrolytes, including calcium and magnesium, and liver function tests should be performed weekly during each cycle. Procarbazine inhibits monoamine oxidase and thus predisposes patients to autonomic sensitivity. Avoidance of foods containing high amounts of tyramine (e.g., red wine, cheese, and tomatoes) and of any sympathomimetic drugs (tricyclic antidepressants, hypnotics, antihista mines, narcotics, and phenothiazines) is necessary during therapy. The nitrosoureas (carmustine and lomustine) can cause hepatic necrosis and pulmonary fibrosis, which are related to cumulative dosing (more than 1,500 mg/m^2). Current recommendations include avoiding nitrosourea therapy in the care of patients with marked pulmonary disease and monitoring of pulmonary function tests every few cycles. Nitrosoureas should be discontinued when a cumulative dose of 1,500 mg/m^2 is attained. Vincristine causes sensorimotor neuropathy and

can produce changes in mental status, result in the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), and diminish levels of phenytoin. Methotrexate-leucovorin may be associated with stomatitis. Cytarabine has been shown to cause cholestasis and mucositis in some patients. Cyclophosphamide can cause a hemorrhagic cystitis, water retention, and alopecia.

VII. Ancillary support

A. Diagnosis and recurrence. With the exception of the more benign tumors (e.g., meningioma, pilocytic astrocytoma, ganglioglioma, and neurocytoma), most primary CNS tumors recur and necessitate terminal care. Because cancer, especially cancer of the brain, is such a devastating diagnosis, it is important to realize and understand the anxiety of the patient and family. Most neurooncologists are members of a multidisciplinary team of physicians, nurses, and social workers who specialize in the care of patients with brain tumors and their families. Each member of the health care team should speak with the patient and concerned family members and provide both practical and emotional support. A mutual understanding of the disease and management of long-term expectations provides a better overall working relationship and maximizes the quality of life for the patient and family. At recurrence, the patient and family may need additional support.

These issues can be addressed by either the nursing or social work staff in addition to the physician. Patient care concerns have to be especially identified in this aspect of treatment. Education is a particularly important aspect of patient care. It includes teaching the patient and family about chemotherapeutic intervention, daily medications, and specific nutritional or equipment requirements. Support staff can act as facilitators in identification and accessing of community resources and services such as home care nursing and cancer support groups.

B. Terminal care. In the United States, once terminal care is needed, it is appropriate to contact local hospice services. Hospice provides the patient and family with emotional support, respite care, equipment, and supply services when death is imminent. The importance of hospice care, in conjunction with frequent contact with the health care team, cannot be overemphasized because of the emotional consequences of such an impending loss. This combination of care can be helpful in making the patient as comfortable as possible and can aid in the transition of the family after death.

LUMBAR DISC DISEASE

Introduction

Lumbar disc disease accounts for a large amount of lost productivity in the workforce. Accurate diagnosis can be difficult and often requires interpretation. Treatment is controversial. Surgical treatment can be technically simple and professionally gratifying for the surgeon. Treatment failures are not uncommon, are often related to posttraumatic or work-related injuries, and may result in litigation. As a consequence, this disease can generate distrust of physicians on the part of patients and vice versa.

History of the Procedure

The first published report of lumbar disc herniation with radiculopathy was written by Mixter and Barr in 1934. Surgical treatment was not widespread until the 1950s. Today, lumbar discectomy is one of the most commonly performed elective operations in western countries.

Problem: Lumbar disc disease is a rather encompassing term. For example, some physicians include back pain alone as a symptom of disc disease. Others make the diagnosis without evidence of disc disease on MRI. The discussion of this article is limited to well-defined lumbar disc herniation. The pathophysiology, clinical presentation, radiographic diagnosis, treatment, and outcome are discussed.

Frequency: Although most people experience back pain during their lifetime, only a fraction experience lumbar radiculopathy or sciatica as a consequence of root compression or irritation. Almost 5% of males and 2.5% of females experience sciatica at some time in their lifetime.

Etiology

A herniated disk fragment comes from the nucleus pulposus of the disc (a remnant of the embryonic notochord). In the normal condition, this nucleus is in the disk center securely contained by the annulus fibrosus.

When a fragment of nucleus herniates, it irritates and/or compresses the adjacent nerve root. This can cause the pain syndrome known as sciatica and, in severe cases, dysfunction of the nerve.

Clinical presentation

Most lumbar disc herniations are preceded by bouts of varying degrees and duration of back pain. In many cases, an inciting event cannot be identified. Pain eventually may radiate into the leg. It may be characterized as less achy, burning, or similar to an electrical shock and is often described as a shooting or stabbing pain. The distribution of the leg pain is somewhat dependent on the level of nerve root irritation. Higher herniations (third or fourth lumbar levels) can radiate into the groin or anterior thigh. Lower radiculopathies (first sacral level) cause pain in the calf and bottom of the foot.

Fifth lumbar radiculopathy, which occurs most commonly, causes lateral and anterior thigh and leg pain. Often, accompanying numbness or tingling occurs with a distribution similar to the pain. Accompanying muscle weakness may be unrecognized if the pain is incapacitating. The pain usually improves when the patient is in the supine position with the legs slightly elevated. Patients are more comfortable when changing positions. Short walks can bring relief. Long walks or extended sitting (especially driving) can aggravate the pain.

On examination, patients may be neurologically normal, may have a profound radiculopathy, or may even demonstrate a cauda equina syndrome. A positive straight-leg raising sign is almost always present. However, a crossed straight-leg raising sign may be even more predictive of a lumbar disc herniation. The back may appear scoliotic. Gait is often abnormal. Muscle weakness may be revealed particularly when testing walking on heels and toes.

Indications

The indications for surgical treatment of symptomatic lumbar disc disease are not clearly delineated. Nevertheless, situations exist in which most spine surgeons would probably agree on operative intervention. These situations include the following:

- A patient with cauda equina syndrome
- A patient demonstrating progressive neurologic deficit during a period of observation
- A patient with persistent bothersome sciatic pain, despite conservative management, for a period of 6-12 weeks (a time period that varies from surgeon to surgeon)

Notably missing from this list is a patient presenting with a profound motor deficit of varying duration. In the absence of pain, whether such patients benefit from surgery is unclear. No consensus has been reached concerning how urgent surgery is for a patient who presents with a clinical picture of painful disk herniation. Unfortunately, the decision to operate emergently is often based on fear of legal repercussions rather than on scientific evidence of actual patient benefit.

Relevant anatomy and contraindications

Relevant Anatomy

A disc herniation most frequently irritates the displaced nerve root. One of the more difficult concepts for beginning medical students to grasp is the anatomic relationship of the fifth lumbar (L5) nerve root to the L4-5 disc herniation.

Equally important to understand is the concept of the far lateral or foraminal disc herniation in which the root above the disc herniation is irritated.

With very large herniations, the entire cauda equina can be compressed and functionally compromised. This causes saddle anesthesia and can cause urinary retention and incontinence.

Contraindications

Any claim of absolute contraindication would invariably be challenged. Most spine surgeons adhere to some guidelines, including the following:

A patient with unrelenting back pain. Patients who have back pain after a bout of sciatica has resolved are not good candidates for operative treatment. Often, these patients are the most insistent and difficult to manage. Occasionally, these are patients whose back pain improved after discectomy for a large central disc herniation.

A patient with an incomplete workup. When diagnosis is uncertain, postpone surgery. Disc herniations are so ubiquitous that being cavalier in diagnosis is easy. Ensure the completeness of the workup prior to proceeding with the operation. All surgeons can recall several cases in which a diabetic plexopathy or an epidural metastasis was missed.

A patient not provided adequate conservative treatment. Spine surgeons rarely commit a patient with a short period of sciatica and without bedrest and a steroid trial to an operation that will permanently alter the patient's back mechanics and strength.

Investigative Studies

Imaging Studies

MRI is by far the most commonly ordered test to evaluate patients with sciatica. Often, MRI is performed prior to plain radiographs. MRI is very sensitive in delineating lumbar disc herniations. Far lateral discs are best evaluated with this test. In reoperations, MRI can delineate the full extent of scar tissue and, with moderate reliability, differentiate it from recurrent disc herniation.

CT scan myelography may be preferred by surgeons for evaluating patients before reoperation or for evaluating patients who have severely spondylotic changes. This is because CT scan myelography can delineate bony structures better than MRI.

Plain radiographs, especially with weight-bearing flexion and extension views, can be a useful adjunct to other radiographic evaluations. Some spine tumors, instabilities, malalignments, and congenital anomalies can be identified best with plain radiographs. Obtain plain films on all patients prior to surgery.

Other Tests

Electromyography is rarely helpful in the diagnosis or management of lumbar disc disease. Occasionally, a diabetic patient can be identified as having a polyradiculopathy or plexopathy. On this basis, some surgeons proceed to surgery with more caution.

Some surgeons continue to submit disc material for histologic diagnosis. The yield of this is exceedingly low and of questionable benefit.

Treatment

Medical therapy

Almost all patients with sciatica and disc herniations deserve a trial of medical therapy. The one obvious exception is a patient presenting with cauda equina syndrome or profound motor deficits.

Most practitioners are well versed in the initial management of cases of sciatica. Counseling and education about the disease helps the patient commit to a successful trial of nonoperative management. Encourage bedrest and prescribe anti-inflammatory agents (steroidal and/or nonsteroidal) with analgesics that are sufficiently strong enough to relieve pain. Muscle relaxants aid in relieving associated muscle spasm. After 7-14 days, slow mobilization is started.

Once the patient has recovered from the worst radicular pain, physical therapy can be instituted. Return to work (either limited or full) is important at this point. Stop steroidal medications. Reevaluate patients about a month after the onset of sciatica. At this time, studies can be ordered or a more intense back rehabilitation program can be designed so appropriate referrals can be made.

Epidural steroid injections can be employed at almost any time.

Surgical therapy

What constitutes surgical therapy is open to discussion. The standard lumbar microdiscectomy has numerous variations. Percutaneous discectomies are still performed frequently. Lately, endoscopic techniques have gained in popularity. Chemonucleolysis, although in principle an excellent alternative, is no longer performed. Other procedures, such as thermal ablation, are also performed.

Preoperative details. A complete workup is essential. Based on the patient's age group and comorbidities, perform the appropriate laboratory examina-

tions, radiographic examinations, and further tests, as needed, to ensure a safe anesthetic period.

Intraoperative details. The standard lumbar microdiscectomy is described. Variations in technique exist between institutions, regions, and surgeons.

The patient is anesthetized and placed in the prone position. The hips are flexed to open the interlaminar spaces. A protuberant belly should hang as freely as possible to reduce venous hypertension. The ulnar nerves at the elbow are padded to prevent neuropathy. The legs cannot be overflexed. The back is parallel to the ground. A preoperative radiograph with a spinal needle is obtained to confirm localization. The back is shaved and prepared.

After injection of a long-acting local anesthetic agent, a 3-cm incision is made over the disc space (as determined by radiograph). Unipolar cautery is used to dissect down through midline subcutaneous fat. The lumbodorsal fascia is opened paramedially. Muscles are stripped from the lamina. Obtain a repeat radiograph to confirm the appropriate location.

A small laminotomy is created with a drill or rongeurs. The ligament is excised with rongeurs or a knife. An operating microscope is now used. The medial facet is partially resected in most patients. The root is then identified and retracted. The disc fragment is evident below the retracted root.

The annulus is incised and the disc removed with pituitary rongeurs. Remove loose fragments of the disc in the space. Palpate the course of the nerve root with an angled instrument along its entirety to ensure adequate decompression. Bleeding is stopped, the wound is irrigated, and then it is closed in interrupted absorbable sutures layer by layer. A light dressing is applied.

Postoperative details. The patient is treated with oral narcotics and IV supplementation for pain. Antiemetics are administered as needed. The patient is mobilized 4-6 hours after surgery and should be able to void without help. Once the patient tolerates fluids, he or she may leave the hospital with an ample supply of narcotics, antispasmodic agents, and stool softeners. Rarely, the patient may remain in the hospital 24 hours after the operation.

Follow-up care. The patient is seen in follow-up one month after surgery. For uncomplicated cases, the patient is then released from the surgeon's care. The patient is usually released to work 6-10 weeks postoperatively, depending on the occupation.

Complications

The overall complication rate is 2-4% for the surgery. Despite endless reports of misadventures, surgeons still operate on the wrong level. Therefore, reliance on intraoperative radiographic confirmation of the intended level is strongly encouraged.

Bleeding intraoperatively can be copious and is almost invariably due to malpositioning. Engorged venous epidural channels can make the operation more difficult and far more dangerous. Very rarely, the anterior annulus is violated and a retroperitoneal vessel is injured. Awareness of this complication is essential. Should this occur, the back is closed while a vascular surgeon prepares to repair the vessel via laparotomy.

Infections, usually skin infections, can occur. The authors' protocol is to administer one dose of a preoperative antibiotic within one hour of surgery. Very rarely, postoperative discitis can cripple a patient who is recovering. Suspect discitis in the setting of an increasing sedimentation rate, fevers, severe localized pain, and recurrent symptoms.

Increased neurologic deficit is usually mild and is due to excessive retraction of the root. If a nerve root is mistaken for a disc herniation and is removed, the resultant injury can be severe. If possible, identify the root and disc in the same field. On occasion, a conjoined root can add significant technical complexity to the case.

Outcome and prognosis

Almost every study measures the outcome from lumbar disc surgery differently. A good outcome may be defined as the decreased use of narcotics, prompt return to work, or reported reduction in pain. Understandably, outcome studies can be misinterpreted or misrepresented.

Approximately 75% of patients who undergo a microdiscectomy have long-term reduction of sciatic pain and, thus, are considered cured. Reported results vary from 65-95%. Predominance of leg pain is the best determinant of good outcome from surgery for lumbar disc herniation.

Unfortunately, a rather large fraction of individuals who have had surgery for lumbar disc disease have recurrent or residual pain, which can be a significant challenge to treat. A methodical postoperative evaluation is necessary, focusing on symptom clarification, careful examination, and repeat radiographic examinations and MRI with contrast.

Also, some patients who are surgically treated are more prone to further problems such as recurrent herniations, arachnoiditis, and vertebral instability.

Future and controversies

The duration of conservative management has been debated since the disease was identified. As surgical treatments become less invasive and medications change, the role and duration of conservative management will change as well. Endoscopic operations are becoming safer and more prevalent. Although many microdiscectomies are now being performed in the outpatient setting, the impetus for even less invasive procedures continues. The role of stabilization in

lumbar disc surgery is very unclear. An increasing number of patients are having extensive fusions as the first-line management of lumbar radiculopathy secondary to disc herniations. However, the indications for stabilization need to be better established.

NEUROLOGIC EXAMINATION

DIFFUSE CORTICAL FUNCTION: MENTAL STATUS

1. LEVEL OF CONSCIOUSNESS

The level of consciousness is the first state evaluated in the neurologic examination. Consciousness may be assessed as normal (patient awake and alert, attentive to surroundings and to the examiner), depressed (patient sleepy, lethargic, stuporous-arousing only briefly in response to pain stimulation; or comatose-not arousable by pain stimulation); or hyperalert (patient distractible, jittery, "jumpy").

2. COGNITIVE FUNCTIONING

Assessment of cognitive functioning aims not to determine "how smart the patient is" but how the patient's cognitive capacity has changed from a recent baseline. The examiner must have some way (recent work history, observations of family, other physicians, etc) of assessing the patient's cognitive status before onset of the present illness. Assessment should include (at a minimum) informal evaluation of the following.

Cognitive Functioning Checklist

A. Orientation to person, place, and time

B. Fund of common knowledge as judged by the response to such questions as "Who is the president?" or "How many nickels are there in a dollar?"

C. Memory. Short-term-name three common objects, then name them again them after 5 minutes; long-term-recount verifiable events from the past.

D. Insight and judgment. "Why have you come to see me?"

E. Concentration. Can often be tested along with calculations (see below) or by instructing the patient (for example) to repeat a series of four to seven digits, arrange the letters in "world" in alphabetical order, or spell "world" backward.

F. Calculations. The conventional test is serial sevens, but informal "real-life" problems may yield a more objective result:

1. Serial sevens. Count backward from 100, taking away 7 each time

2. Real-life problem. For example, "If an apple costs 20 cents, how many can you buy for $1.50?" Then, "How much change do you have left over?"

G. Abstract thought. Examples are proverb interpretation or "compare-and-contrast" tasks such as, "How is an apple different from-[or the same as]-an orange?"

H. Verbal fluency. Can be judged by listening to the patient talk or by asking such questions as, "How many words can you say that start with the letter B?" (Time for 30 seconds.)

I. Other. The examiner should now be able to form an impression of the patient's mood, content of thought, and appropriateness of behavior.

FUNCTION OF SPECIFIC HEMISPHERES

1. DOMINANT HEMISPHERE

The most important function of the dominant hemisphere is language. Language skills include comprehension, repetition, naming, reading, and writing. Language mastery can be lost as a consequence of diffuse transient (eg, metabolic derangements) or degenerative disease (eg, dementia), but language impairment with otherwise normal cognitive function almost always suggests a focal lesion.

Aphasias

Impairments of the expression or understanding of language are traditionally divided into categories depending on the pattern of the language deficit and the site of the damage. There are three most frequently seen syndromes of clinical significance: Broca's aphasia, Wernicke's aphasia, and conduction aphasia. The three syndromes are tested for as follows.

A. Fluency. Listen to spontaneous speech. Assess for fluency, errors of grammar or vocabulary, neologisms (meaningless words), or word substitutions (paraphasias). Determine whether the patient's speech makes sense in the current context. Alternatively, give the patient paper and pencil and say, "Write your name." "Write, The boy and the girl are happy about the dog." "Please write down your reason for being here."

B. Comprehension. Using only words (no gestures), instruct the patient to follow commands of increasing complexity: "Close your eyes." "Show me your left hand." "With your left hand, put a finger in your right ear." Alternatively, present a written command ("Go to the door, knock three times, and come back") and assess whether the task is performed properly. If the patient does not comply, assess cooperation and physical capacity by repeating the commands with demonstration and miming.

C. Repetition. Ask the patient to repeat three common nouns ("bread, coffee, pencil") and then to say, "No ifs, ands, or buts."

D. Writing

With rare exceptions, every patient aphasic in speech is also aphasic in writing (agraphic). A patient who cannot speak but can write is mute, and the lesion is not in Broca's area. Muteness occurs in a wide variety of disorders, including severe rigidity, vocal cord paralysis, bilateral corticobulbar lesions, and psychiatric disease.

E. Naming

Difficulty in naming familiar objects (anomia) may occur in expressive aphasia or other aphasic syndromes but by itself is not diagnostic of any specific entity. It is more likely a consequence of diffuse cerebral dysfunction of structural or metabolic origin. Ask patients to name or mute patients to point to a wrist watch, a typewriter keyboard, etc.

2. THE NON DOMINANT HEMISPHERE

Tests for lesions of the nondominant hemisphere are chiefly concerned with the interpretation of incoming stimuli (other than language), visuospatial orientation, and perception of the contralateral body in space. (Lesions of the dominant hemisphere can also produce abnormalities in these areas, but they are usually masked by aphasia.)

Assessment of Sensory

Interpretation

Defects of sensory interpretation can be evaluated in a number of ways, though all require reasonably intact primary sensation.

A. Graphesthesia. Ask the patient to identify a letter or number written on the palm.

B. Object identification (stereognosis). Have the patient name a common object placed in the hand (key, paper clip, coin, etc).

C. Neglect. Misperception of one side of space results in a number of abnormalities collectively called neglect. The patient may not heed information incoming from the side contralateral to the lesion (right brain affecting left side of body). For example, the patient may hunt eagerly for the examiner's face on the right when the voice is calling from the left – or may eat only the food on the right side of a plate. Patients may deny that the left side of the body exists (even a dense hemiparesis may be cheerfully "overlooked"), fail to acknowledge as one's own the left arm held up in plain view by the examiner, or, most dramatically, fail to properly clothe or groom the left side of the body. Clumsiness or "disuse" out of proportion to actual weakness-or a pronounced lag in initiating

movement on the involved side-suggests motor **apraxia** as a manifestation of neglect. There are several classic tests, as follows.

Spatial Orientation

Approach the patient quietly on the weak side (particularly when the head and gaze are turned away), enunciate a greeting and observe whether the patient's head turns ("orients") to the source of the voice or searches only on the wrong side. Then move over to the "good" side and repeat the exercise.

Double Simultaneous Stimulation

Touch the patient gently first on one hand and then the other while identifying the side. Then randomly vary the stimulus, asking the patient to say, with both eyes closed, "left," "right," or "both." Mute patients should be asked to raise the touched hand. If the patient correctly identifies each side in isolation but "extinguishes" the touch on the involved side when both are touched, neglect is present.

Clockface Exercise

Draw (or have the patient draw) a large circle and ask the patient to write in the numbers of the hours of the day. Note if the patient writes all 12 numbers into the hemicircle opposite the neglected side. If the numbers are placed correctly, the patient should then be asked to draw in the hands to indicate a specified time such as "a quarter to four."

Reading, Writing

Ask the patient to read from a book or write on a sheet of paper. The patient may read only the right side of the page or squeeze the sentence into the right half. Give the patient a sheet of lined notebook paper and say, "Cross out all the lines." Note whether lines on the left side of the page are ignored.

Ideomotor Apraxia

Ask the patient to manipulate some familiar object (dial a phone number, hold a pencil in the position of writing) or to raise one arm in the air.

CRANIAL NERVES

1. OLFACTORY (I)

Ask the patient to identify common scents such as coffee, vanilla, etc, with eyes closed. Do not use irritants. In testing olfactory nerve function, it is less important to determine whether the patient can correctly identify a particular odor than whether the presence or absence of the stimulus is perceived.

2. OPTIC (11)

Visual Acuity

A pocket card or wall chart – or any reading matter – may be used to observe the focal distance (normally, small newspaper print can be read at 32 inches). Patients with refractive errors may wear spectacle lenses or be given a pinhole.

Visual Fields

Visual fields are a measure of the integrity of the optic nerves and the postthalamic optic radiations through the hemispheres. They are tested as follows.

A. Confrontation Testing. Patient and examiner stand at eye level at about arm's length. Have the patient cover the left eye. With right arm extended and then brought forward from the side, have the patient say how many fingers are shown. The patient and examiner should see the fingers at the same time. Then repeat with the left hand to the patient's right eye. Test all four quadrants in each eye in this way.

B. Threat Testing. Flick an extended finger obliquely toward the patient's pupil from each temporal field and observe for blinking. This crude test is occasionally useful when the patient is less than fully alert or is uncooperative.

Fundus (Ophthalmoscopic) Examination

Look for blurring of the disk margins, loss of venous pulsations, retinal lesions, abnormalities of the vessels, and color of the optic nerve head.

3. PUPILLARY REFLEXES (II, III)

A normal pupil will constrict (1) in response to direct light, (2) as a consensual response to light in the opposite eye, and (3) to accommodation (convergence to focus on a close object). A pupil that reacts to accommodation but not to light is an Argyll-Robertson pupil, signifying a lesion in the tectum of the midbrain. A Marcus-Gunn pupil is one with impaired constriction to direct light with preservation of the consensual response; in this case, an afferent light stimulus does not reach the lateral geniculate nucleus and a lesion should be sought in the optic tract, preoptic chiasm, optic nerve, or retina.

Constriction to Accommodation

The patient is instructed to gaze at the wall over the examiner's shoulder and then quickly focus on the examiner's forefinger held in front of the patient's nose. Look for subtle constriction when the patient changes from far vision to very near. To see the constriction, use a dimmer light, held obliquely.

Consensual Constriction (Swinging Flashlight Test)

After shining a flashlight into one eye to constrict the pupil, switch to the other eye and observe if that pupil constricts further (normal response) or dilates (abnormal response).

4. CONTROL OF EXTRAOCULAR MUSCLE MOVEMENTS

Extraocular muscle movements are controlled by the oculomotor (III), trochlear (IV), and abducens (V) nerves-innervating the lateral, medial, superior, and inferior rectus muscles (LR, MR, SR, IR) and the superior and inferior oblique muscles (SO, 10).

Movements need to be checked in all six directions of gaze: LR (VI) for lateral gaze, MR (III) for medial gaze, IR and SR (III) for down gaze and up gaze with the eye laterally deviated, and SO (IV) and 10 (III) for down gaze and up gaze with the eye medially deviated. Ask about diplopia, as the patient's perception is more sensitive than the examination results.

Abnormalities of eye movements can result from lesions other than those involving the cranial nerves-anything from muscular or neuromuscular disease to central lesions in the cortex or brain stem. For example, if the patient has had a stroke, horizontal movements may remain conjugate (with eyes moving smoothly yoked together) but gaze at rest may be directed to one side-toward the lesion if the lesion is cortical, away from the site of damage if the lesion is in the brain stem.

If the patient is unresponsive or otherwise unable to perform voluntary eye movements, the doll's eye (doll's head) maneuver (oculocephalic reflex) should be performed (see below).

Nystagmus is rhythmic oscillation of the eyes; it can be either conjugate or asymmetric. It can be a normal phenomenon (eg, at the extremes of lateral gaze) or may relate to weakness of an eye muscle or to lesions in the brain stem, cerebellum, or anywhere in the peripheral or central vestibular systems; each type has its characteristic pattern. Nystagmus is most easily observed-as are all disorders of smooth coordinated eye movements-while the patient is following the examiner's finger.

Tests for control of extraocular muscle movements include the following.

Primary Gaze (Straight Ahead)

Look for symmetry of position of the light reflection off the two corneas.

Volitional Eye Movements

Face the patient and put a hand on the patient's forehead and say, "Follow my finger, just with your eyes." Then move the index finger of the other hand horizontally, then up and down on either side, tracing the letter H.

Doll's Head (Oculocephalic) Maneuver

The patient's head is held firmly and rotated from side to side, then up and down. (It may be necessary to hold the eyelids open as well.) If the brain stem is intact, the eyes will move conjugately away from the direction of turning (as if still looking at the examiner rather than fixed straight ahead).

5. TRIGEMINAL NERVE (V)

Facial Sensation

Simultaneously touch both sides of the forehead, then the cheek, and then the jaw and ask if they feel the same. Check for temperature perception in the same sequence, using the cool surface of a tuning fork or other appropriate stimulus. The stimulus will be perceived as warmer on the side of impaired sensation.

Corneal Reflex

Sweep a wisp of cotton lightly across the lateral surface of the eye (out of the direct visual field) from sclera to cornea. As soon as the stimulus reaches the sensitive cornea, the patient will wince and blink vigorously if nerves V and VII are both intact. Compare the sides for symmetry.

Motor V Testing

Observe the symmetry of opening and closing of the mouth; the jaw will fall faster and farther on the side of the lesion, so that the face looks askew. For more subtle weakness, ask the patient to clench the teeth and then attempt to force jaw opening or lateral jaw displacement. Normal strength cannot be overcome.

6. FACIAL STRENGTH (VII)

A central "supranuclear" lesion, such as a hemispheric stroke, will preserve forehead wrinkling and cause only mild weakness of eye closure, while the lower face is more severely involved. If there is a peripherallesion of the cranial nerve (or nucleus), the entire hemiface will be flaccid and the eyelids will gape open.

Some cranial neuropathies or neuromuscular diseases cause bilateral facial weakness, and in such cases the usual criterion of facial asymmetry as a marker of weakness will not apply.

Facial Symmetry

Observe the patient's face for symmetry of the palpebral fissures and nasolabial folds at rest. Ask the patient to wrinkle the forehead, then to squeeze the

eyes tightly shut (looking for asymmetry in the extent to which the eyelashes protrude), then to smile or snarl, saying, "Show me your teeth."

Bilateral Facial Weakness

Ask the patient to squeeze the eyes tightly shut, then press the lips tightly together, then puff air into the checks. If strength is normal, one should not be able to pry the eyelids open, force the lips apart, or forcibly expel air from the mouth.

7. AUDITORY (VIII)

Auditory acuity can be tested crudely by rubbing thumb and forefinger together about 2 inches from each ear. If there are complaints of deafness or if the patient cannot hear the finger rub, proceed to the following tests.

Rinne Test

Hold the base of a lightly vibrating high-pitched (512 Hz) tuning fork on the mastoid process until the sound is no longer perceived, then bring the still vibrating fork up close to (not touching) the ear. Normally-or if the hearing loss is sensorineural-air conduction is greater than bone conduction and the patient will again hear the tone. If there is significant conductive loss, the patient will not be able to hear the air-conducted tone longer than the bone-conducted tone.

Weber Test

Lightly strike a high-pitched (512 Hz) tuning fork and place the handle on the midline of the forehead. If there is conductive loss, the tone will sound louder in the affected ear; if the loss is sensorineural, the tone will be louder in the unaffected ear.

Vestibular Function

Vestibular function needs to be tested only if there are complaints of dizziness or vertigo or evidence of nystagmus. The Nylen-Barany (Dix-Hallpike) maneuver tests for positional vertigo. In this disorder, as in other types of vertigo of peripheral origin, nystagmus will come on after at least 3-5 seconds, will decrease with time, and will become less prominent with repetition of the test.

Nylen-Barany (Dix-Hallpike) Maneuver

The patient sits with legs extended on a table while the examiner supports the head and shoulders. Rapidly lower the patient to the supine position with neck hyperextended (head hanging off the table) and rotated to one side; repeat with the head turned to the other side. Look for nystagmus and ask the patient to report vertigo. The patient may need encouragement to keep the eyes open.

8. GLOSSOPHARYNGEAL (IX) & VAGUS (X)

Some useful tests for detection of deficiencies in motor function of the palate, pharynx, and larynx are described below. Sensory function needs to be checked if one suspects cranial neuropathy or a brain stem lesion.

Palatal Elevation

Ask the patient to say "ah". Look for full and symmetric palatal elevation (not deviation of the uvula). If one side is weak, it will fail to elevate and will be pulled toward the strong side.

Gag Reflex (Afferent IX, Efferent X)

Gently touch each side of the posterior pharyngeal wall with a cotton swab and compare the vigor of the gag.

Sensory Function

Lightly touch each side of the soft palate with the tip of a cotton swab.

Voice Quality

Listen for hoarseness or "breathiness," suggesting laryngeal weakness.

9. ACCESSORY (XI)

Sternocleidomastoid

Press a hand against the patient's jaw and have the patient rotate the head against resistance. Pressing against the right jaw tests the left sternocleidomastoid and vice versa.

Trapezius

Have the patient shrug shoulders against resistance and assess weakness.

10. HYPOGLOSSAL (XII)

Dysarthria is a defect in the mechanical production of speech sounds. Testing for dysarthria provides a quick functional assessment of the lower cranial nerves, cerebellum, and basal ganglia. Facial weakness (see VII above) can be assessed by asking for labial sounds ("mee-mee-mee"). Pharyngeal weakness (see IX and X above) results in a nasal voice as assessed by asking for guttural sounds ("kay-kay-kay"). Laryngeal dysfunction (see IX and X above) presents as hoarseness or "breathy" speech. Maximal difficulty is found with a high-pitched sound, as this requires vocal cord adduction. Tongue weakness (XII) is manifested by pronounced slurring, particularly of lingual sounds ("la-la-la"). Bilateral corticobulbar tract lesions are manifested by strangled, spastic, labored

speech or, if severe enough, no speech at all (along with inability to open the mouth or protrude the tongue and a hyperactive gag reflex).

Tests for hypoglossal nerve function include the following.

Atrophy or Fasciculations

With the patient's tongue resting in the floor of the mouth, first inspect for atrophy or fasciculations (worm-like quivers and twitches). Then ask the patient to protrude the tongue, and observe for deviation to the weak side. Be sure the deviation is real and not just apparent because of facial weakness. Mark the midline of nose and chin with thumb and forefinger. Then ask the patient to move the tongue rapidly from side to side.

Subtle Weakness

If subtle weakness is suspected, have the patient push the tongue into each cheek against external resistance. Strength of protrusion to one side is a measure of the power of the opposite hypoglossal muscle.

Subtle Dysarthria

Ask the patient to repeat difficult phrases such as "methodist episcopal" or "administrative assistant."

MOTOR COORDINATION

The cerebellar hemispheres are responsible for coordinating and fine-tuning movements already set in motion and for correcting speed, accuracy of direction, and intensity of force to meet the intended purpose. The cerebellar hemispheres control the ipsilateral appendages, particularly the arms.
The following are some tests for cerebellar hemispheric function.

Finger-to-Nose

Ask the patient to alternately touch his or her nose and then the examiner's extended forefinger, held far enough away to require reaching. Look for overshoot or for an oscillatory "hunting" tremor that increases in amplitude as the target is neared. Abnormalities are referred to as dysmetria.

Finger-Tapping, Toe-Tapping

Demonstrate and then ask the patient to tap as evenly and rhythmically as possible. Look and listen for irregularities of rhythm or force.

Rapid Alternating Movements

Have the patient strike the thighs rhythmically and rapidly, alternating between the palms and the backs of the hands; rapidly touch the thumb to each finger in succession; or rapidly wiggle the protruded tongue from side to side.

Dysdiadochokinesia is the technical term for dysrhythmias in performing any of these tasks.

Rebound

The patient flexes an arm as strongly as possible or holds the arm extended against resistance. The examiner then suddenly lets go. If the arm flies upward or toward the face, this signifies that the patient is unable to check the abrupt imbalance between flexors and extensors.

Heel-Knee-Shin

The supine or seated patient is instructed to place one heel against the opposite knee, tap the knee with the heel, then run the heel smoothly down the tibia to the ankle.

Cerebellar Vermis

The cerebellar vermis is concerned with postural stability and axial function-particularly stance and gait. In patients with lesions in this area, the gait will be wide-based and ataxic (staggering) and it may be difficult to sit upright without support. There may be irregular back-and-forth rocking or shaking of the head (titubation), and speech may be "scanning," ie, irregular in force and pitch, with words distinctly broken into "syl-luh-bles." Integrity of the vermis can be tested by asking the patient to stand "naturally" while one observes how far apart the feet are positioned for a stable base. The examiner then extends the arms (for reassurance and to prevent falls) and asks the patient to bring the feet together until they touch.

Basal Ganglia

Disorders of the basal ganglia (extrapyramidal system) may result in inability either to initiate motor activity (bradykinesia, loss of associated movements such as arm swinging), correct for postural imbalance, or control movements such as tremor or chorea. Tremor or other abnormal movements should be observed with the patient at rest, during arm extension, and during performance of a goal-directed action such as drinking from an imaginary cup.

Other Tests of Motor Coordination

A. Turning Around. How many steps does the patient need to "about face"? A normal turn is made with a one- or two-step pivot. A patient with parkinsonism may require up to 20 small steps ("en bloc turn") or may freeze altogether.

B. Drawing Spirals. The patient is asked to draw a copy of an expanding (Archimedes) spiral. In parkinsonism, there is difficulty enlarging the figure's successive loops.

C. Retropulsion. The examiner stands behind the patient, announces what is about to happen, then vigorously pulls the patient backward by the shoulders. Normally, the subject will regain the center of gravity with a step or two backward and truncal flexion. The patient with parkinsonism cannot do so and may stagger rigidly backward or fall into the examiner's arms.

MOTOR FUNCTION

The motor examination includes evaluation of muscle tone, bulk, and strength.

1. MUSCLE TONE

Tone is defined as resistance of muscle to passive movement at a joint. Tone can be decreased, normal, or increased.

The hardest part of evaluating tone is getting the patient to relax. Diversionary tactics may be required. Once the patient is seen to be relaxed, the following maneuvers can be used.

Arm Muscle Tone

Support the patient's bent arm with one hand cupping the elbow, then smoothly flex and extend the forearm, then pronate and supinate. Grasp the forearm and flop the wrist back and forth, briskly raise the arms as if tossing them into the air, and then abruptly let go and watch how fast and symmetrically they drop.

Leg Muscle Tone

With the patient lying prone and relaxed, place a hand under the knee, then abruptly pull vigorously upward. With normal or reduced tone, the heel lifts only momentarily off the bed or remains in contact with the surface as it slides up toward the buttocks. The hypertonic leg lifts off the bed. With the patient seated, grasp the knee and bounce the foot up and down off the floor.

Axial Rotation

Passively rotate the patient's head and observe if the shoulders also move, or gently but firmly flex and extend the neck and assess resistance.

2. MUSCLE BULK

Some loss of muscle bulk may be seen with disuse, but significant atrophy ("wasting") is characteristic of denervation from lower motor neuron lesions. Atrophy may also be associated with fasciculations, or rapid twitching. These

spontaneous contractions of a muscle fascicle may resemble worm-like writhing under the skin, or occasionally may be coarse enough to move a small joint. Asymmetric atrophy can best be assessed by comparing sides or by careful measurement when in doubt. If atrophy is diffuse, one can compare the patient's muscle to a "normal" muscle by palpating one's own corresponding muscle mass.

3. MUSCLE STRENGTH

Strength is measured by the ability to contract the muscle against force or gravity. The classic grading system scores as follows: 5, full strength; 4, movement against gravity and resistance; 3, movement against gravity only; 2, movement only if gravity is eliminated (eg, horizontally along the surface of the bed); I, palpable contraction but little visible movement ("flicker"); 0, no contraction.

Exactly which muscles are tested-and how carefully-will depend on the patient's complaints and the examiner's suspicions. Tests of strength should be conducted with the following in mind:

(I) "Normal" means "to be expected of this patient." A frail elderly man is expected to be less strong than a young weight lifter.

(2) The examiner should be on equal footing with the patient. If testing shoulder abduction, the examiner should stand facing the patient and use only the upper arms to oppose the patient rather than standing above a seated patient and pressing down with full body weight. When testing finger extension, only the equivalent finger should be used, not the whole arm and shoulder strength.

(3) The patient is a more sensitive observer than the examiner and may have more subtle weakness than is detectable through formal testing. This is particularly true in the legs. If indicated, follow formal testing with "functional" tests such as squatting and rising, walking on the heels, and rising from a low stool with arms crossed.

A pattern frequently seen after a stroke is pyramidal weakness, in which abductors and extensors of the arm and flexors of the leg are preferentially affected, so that the arm has a tendency to be held in adducted flexion and the leg in adducted extension.

Tests of strength are as follows.

General Strength

Isolate the specific agonist muscle action and then apply an equal and opposite force in gradually increasing intensity. For example, support the patient's elbow with one hand underneath and attempt to extend the arm by pressing down on the forearm, telling the patient to "bend your elbow up as tightly as you can-don't let me pull it down."

Pyramidal Weakness

Check for weakness of finger or forearm extension by attempting to push down the extended fingers or flex the half-extended elbow. In contrast, the strength of the biceps or hand grip is an insensitive index of pyramidal weakness.

Pronator Drift

Ask the patient to hold the arms straight out with palms up and then to close the eyelids. A weak arm will begin to drift downward and the hand will begin to pronate.

SENSORY FUNCTION

A basic screening examination should assess both large-fiber and small-fiber modalities in the fingers and toes.

1. LARGE-FIBER & DORSAL COLUMN FUNCTIONS

Lesions of large fiber nerves and of the dorsal column of the spinal cord are investigated by tests of vibration and joint position sense. Normal joint position sense is exquisitely sensitive, and the patient should detect any movement no matter how fine. If joint position sense is diminished distally, test more proximal limb joints. Functional tests for joint position sense include Romberg's test and the finger-to-finger test.

Vibration Sense

Strike a low-pitched (128 Hz) tuning fork gently and place the base firmly on a bony prominence, with one finger of the other hand supporting the digit and serving as a control. Ask if the patient "feels the buzz," and determine when it can no longer be perceived. Compare sides, and if sensation is decreased at the toe, repeat at the ankle, knee, or hip to determine the extent of impairment. Compare leg and arm sensation as well. Abnormalities in the distallegs but not the arms are found in patients with polyneuropathies or lesions of the thoracolumbar spinal cord.

Joint Position Sense

Grasp the sides of the distal phalanx of a finger or toe and displace the tip up or down. Rehearse first with the patient watching, then test with the patient's eyes closed to determine the threshold for correctly perceiving the direction of movement.

Romberg's Test

Instruct the patient to stand with the feet as close together as possible. (If the patient cannot stand with the feet together, a cerebellar lesion is present and Romberg's test is not applicable.) The patient is then observed with eyes closed. An abnormal result consists of swaying or other evidence of instability.

Finger-to-Finger Test

Instruct the patient to bring the extended forefingers together with eyes closed through two or three feet of space, or have the patient touch the tip of the nose with a finger. As in the Romberg test, the patient is demonstrating "pseudoataxia," a disorder of sensory input, if finger placement is clumsy with the eyes closed but not with eyes open.

2. SMALL-FIBER & SPINOTHALAMIC FUNCTION

Temperature Sensation

Using the cold flat disk of a tuning fork or other cold object, first establish the patient's ability to detect its temperature in a presumably normal area. Then have the patient compare the relative temperature of the stimulus from the dorsum of the feet upward, or from side to side, or between dermatomes.

Superficial Pain Sensation

Use a disposable instrument, such as a safety pin, for each patient. Prick the skin with enough force to be unpleasant but not harmful, and ask if the prick feels sharp or "hurts like a pin." As always, work from side to side, distal to proximal, or dermatome to dennatome – and from area of deficit toward nonnal regions.

Light Touch Sensation

The sensation of light touch is served by both the large fiber – posterior column system and the small fiber – spinothalamic system. Testing is done with a very light stimulus such as a wisp of cotton, the teased-out tip of a cotton swab, or a brush motion with the examiner's fingertips. Ask the patient to tell with closed eyes where the stimulus is perceived.

REFLEXES

1. DEEP TENDON REFLEXES

A deep tendon reflex is the reaction of a muscle to being passively stretched by percussion on the tendon. These reflexes are a measure of the integrity both of the afferent and efferent peripheral nerves and of their central inhibi-

tory controls. Tendon reflexes are graded on a scale according to the force of the contraction or the minimum force needed to elicit the response: 4, very brisk, often with clonus (record the number of beats); 3, brisk but nonnal; 2, nonnal; I, minimal; 0, absent.

In some cases, deep tendon reflexes are difficult to elicit without such reinforcement as having the patient clench the opposite fist or interlock the fingers and attempt to pull them apart. Hypoactivity or hyperactivity is generally of less significance than asymmetry; however, absent reflexes may be a clue to an unsuspected neuropathy, and hyperactivity may be associated with spasticity.

The four most commonly tested tendon reflexes are described here.

Biceps Reflex (C5-6)

Support the patient's partly flexed elbow with one cupped hand, thumb positioned on the biceps tendon. Strike the thumb with a percussion hammer and assess the force of flexion at the elbow.

Triceps Reflex (C7-8)

Support the patient's partly flexed arm by holding the forearm against the patient's body, or suspend the abducted arm just above the elbow so that the forearm dangles freely. Strike the triceps tendon just above the elbow and assess the force of extension at the elbow.

Quadriceps (Patellar, Knee Jerk) Reflex (L3-4)

The patient's feet can remain on the floor, but it is easier to elicit this reflex if the patient crosses one leg and lets the foot dangle. If the patient is in bed, support the leg in partial flexion with one arm under the knee. Feel for the bottom edge of the patella and strike just below it. Assess the force of extension at the knee.

Achilles (Ankle Jerk) Reflex (S1-2)

The patient's foot is passively dorsiflexed, resting its weight on the ball of the foot, or by pressing on the sole. Strike the tendon or the sole directly. Assess the force of extension at the ankle.

2. BABINSKI SIGN

In patients over age 18 months, the nonnal response to stimulation of the lateral sole is plantar flexion of the toes. Extension upward of the great toe (Babinski sign) is a sensitive but nonspecific sign of central nervous system disease and can be a consequence of pyramidal tract damage or diffuse cerebral dysfunction.

The foot should be held finnly and the patient told what to expect. Place the tip of a suitable instrument, such as the bare end of a swabstick, on the lat-

eral aspect of the sole at the heel and sweep it finnly forward to the base of the toes. Apply the least pressure necessary to evoke a response. A void stroking across and under the toes, a maneuver that might evoke a conflicting (foot grasp) response manifested by flexion of the toes.

3. FRONTAL RELEASE SIGNS

Frontal release signs are primitive reflexes that can be thought of as adaptive for the infant, such as grasping or sucking, but which disappear as the brain matures. Diffuse neuronal dysfunction, especially frontal lobe damage, releases them from inhibition. The more important signs are grasp, or curling of the fingers in response to stimulation of the palmar surface of the hand and fingertips (it can be seen in the foot as well); suck; snout, or pursing of the lips; and the glabellar sign, or persistent blink response.

Grasp Sign

The grasp response is elicited by lightly drawing one's fingertips along the central aspect of the patient's palm and then transversely across the fingertips, gently lifting. This test is performed while the patient is distracted. In a pronounced grasp response, the patient's fingers will hook around the examiner's firmly. Even the touch of an inanimate object such as a chair arm may elicit a tenacious grasp.

Suck Sign

This sign is elicited by gently stroking the patient's lips with the fingers or with a tongue depressor. Sucking or swallowing movements constitute a positive response. The same responses may occur at the mere sight of an approaching finger.

Snout Sign

With an index finger positioned vertically over the lips, tapping the finger with the other hand or with a reflex hammer normally elicits protrusion of the lips. An abnormal response is exaggerated protrusion.

Glabellar Sign

This sign is elicited by repetitive tapping between the patient's eyebrows. The normal response is to blink a few times and then stop. The response is abnormal if the patient continues to blink with each tap as long as the stimulus continues. The glabellar sign may also be present in extrapyramidal disorders.

4. PATHOLOGIC REFLEXES

Pathologic reflexes appear with upper motor neuron damage and consequent loss of inhibition. If tendon reflexes are hyperactive (particularly if asymmetric) or if spasticity is found, these pathologic reflexes need to be sought-though they are not in themselves diagnostic of disease and may in fact be present in normal individuals. Pathologic reflexes include the crossed adductor, finger flexor, jaw jerk, and clonus reflexes.

Crossed Adduction Reflex

Place a hand on the patient's thigh adductor tendon just above and medial to the knee and strike briskly. Normally, only the struck leg will adduct. With upper motor neuron lesions, both legs may adduct and the patient's legs may make a scissoring motion.

Finger Flexor Reflex

Let the patient's arm and hand relax on the bed or table. With thumb and forefinger, pick up the patient's hand so that it dangles with the wrist dorsiflexed and the fingers partly flexed. With the other hand, "snap" the nail of the patient's middle finger with the thumbnail or strike sharply with a reflex hammer against the fingers holding the hand. An abnormal response consists of adduction and flex ion of the thumb and exaggerated flexion of the fingers.

Jaw Jerk Reflex

With an index finger on the patient's relaxed chin, strike the finger downward with a reflex hammer. Exaggerated contraction of the masseter suggests bilateral pathology above the mid pons.

Clonus

Clonus is repetitive, rhythmic, involuntary contraction induced by sudden passive stretching of a muscle or of its tendon. It may occasionally occur spontaneously or be induced in response to a mild stimulus such as the weight of the bedclothes. It is most often seen at the ankle after strong and sustained dorsiflexion.

To elicit ankle clonus, grasp the foot firmly, push sharply upward against the sole, and maintain the pressure. A few beats of alternating flexion and extension of the foot are occasionally seen in normal individuals, but sustained clonus (five or more beats) is abnormal.

STANCE & GAIT

Watching the patient walk may be the most important part of the neurologic examination. Seeing how the patient initiates a planned action, evaluat-

ing the ability to maintain balance while "repetitively hurling oneself into space"-as the act of walking has been described-and analyzing an abnormal gait for clues to the nature of the deficit all provide valuable information.

The minimal screening examination should include evaluation of the following: (1) "Normal" gait across the room. (2) "Heel-walking" with ankles dorsiflexed. (3) "Toe-walking" on the balls of the feet with heels elevated. (4) "Tandem" gait, in which the patient puts one foot directly in front of the other, heel to toe, and walks an imaginary line.

Some characteristic stances and gaits are as follows.

Steppage Gait ("Foot Drop")

Steppage gait is inability to dorsiflex the foot. The patient compensates by exaggerated elevation of the flexed hip and knee to allow the foot to clear the ground while walking. This abnormality is usually the result of a peripheral nerve disorder such as a peroneal palsy or other neuropathy, but occasionally it results from a radiculopathy or central lesion.

Cerebellar Gait

This is a wide-based, irregular, staggering, or reeling gait, as if drunk.

Sensory-Ataxic Gait

A wide-based, short, uneven gait characterized by high steps and slapping down of the feet is seen with proprioceptive loss, as in tabes dorsalis. The eyes may remain "glued" to the ground.

Hemiplegic Gait

With the affected spastic leg extended and internally rotated and the foot in inversion and plantar flexion, the leg circumducts at the hip to allow the foot to clear the floor.

Paraplegic Gait

A slow, stiff shuffling gait with the toes scraping and the legs "scissoring" because of increased adductor tone associated with spasticity is seen in myelopathy or other bilateral corticospinal tract disease.

Dystrophic Gait

Waddling and lordotic posture may result from pelvic muscle weakness.

Parkinsonian Gait

This consists of slow-starting, short shuffling steps with a tendency to accelerate ("festinate") as if chasing the center of gravity. The posture is stooped, turns are "en bloc" with the feet moving only in tiny steps, and there is loss of

normal associated movements, such as arm swinging, that help to maintain balance.

Apraxic Gait

Apraxia consists of inability to execute a learned motor program. Gait apraxia is loss of the ability to walk and results from diffuse cerebral damage-more specifically, damage to the frontal lobe-despite normal strength and coordination. The gait is similar to a parkinsonian gait, but if severe the patient will simply stand, partially upright, unable to "remember" how to go about walking, the feet seeming to be "glued to the floor." Alternatively, the patient will lift and lower the feet without advancing, as if drawn to the floor by magnetic force.

Antalgic Gait

Antalgic gait is a response to pain-favoring one leg by putting as little weight as possible on it.

Choreic Gait

Choreic gait is described as lurching, "jerky twitching," and "dancing." Falls are surprisingly rare.

LUMBAR PUNCTURE

Indications

Lumbar puncture is indicated for the following purposes:

1. Diagnosis of meningitis and other infective or inflammatory disorders, subarachnoid hemorrhage, hepatic encephalopathy, meningeal malignancies, paraneoplastic disorders, or suspected abnormalities of intracranial pressure.
2. Assessment of the response to therapy in meningitis and other infective or inflammatory disorders.
3. Administration of intrathecal medications or radiologic contrast media.
4. Rarely, to reduce cerebrospinal fluid (CSF) pressure.

Contraindications

1. Suspected intracranial mass lesion. In this situation, performing a lumbar puncture can hasten incipient transtentorial herniation.
2. Local infection overlying the site of puncture. Under this circumstance, cervical or cisternal puncture should be performed instead.
3. Coagulopathy. Clotting-factor deficiencies and thrombocytopenia (below 20,000/mm^3 or rapidly falling platelet counts) should be corrected before lumbar puncture is undertaken, to reduce the risk of hemorrhage.
4. Suspected spinal cord mass lesion. Lumbar puncture in this case should be performed only in association with myelography, which is used to determine the presence and level of structural spinal pathology.

Preparation

A. Personnel. With a cooperative patient, lumbar puncture can generally be performed by one person. An assistant can be helpful in positioning the patient and handling CSF samples, of course, especially if the patient is uncooperative or frightened.

B. Equipment and Supplies. The following items, which are usually included in preassembled lumbar puncture trays, are required. All must be sterile.

1. Gloves.
2. Iodine-containing solution for sterilizing the skin.
3. Sponges.
4. Drapes.
5. Lidocaine (1 %).
6. Syringe (5 mL).
7. Needles (22- and 25-gauge).

8. Spinal needles (preferably 22-gauge) with stylets.
9. Three-way stopcock.
10. Manometer.
11. Collection tubes.
12. Adhesive bandage.

C. Positioning. Lumbar puncture is usually performed with the patient in the lateral decubitus position, lying at the edge of the bed and facing away from the person performing the procedure. The patient's lumbar spine should be maximally flexed to open the intervertebral spaces. The spine should be parallel to the surface of the bed and the hips and shoulders aligned in the vertical plane.

Occasionally, it is desirable to perform lumbar puncture with the patient seated. In this case, the patient is seated on the side of the bed, bent over a pillow that rests on a bedside table, while the physician reaches over the bed from the opposite side to perform the procedure.

D. Site of Puncture. The usual practice is to enter the L3-4 or IA-5 interspace, since the spinal cord (conus medullaris) terminates at about the L1-2 level in adults. Thus, the procedure is performed without danger of puncturing the cord. The L3-4 interspace is located at the level of the posterior iliac crests.

Procedure

1. If a comparison between blood and CSF glucose levels is planned, venous blood is drawn for glucose determination. Ideally, blood and CSF glucose levels should be measured in samples obtained simultaneously after the patient has fasted for at least 4 hours.
2. The necessary equipment and supplies are placed within easy reach.
3. Sterile gloves are worn by the person performing the procedure.
4. A wide area surrounding the interspace to be entered is sterilized, using iodine-containing solution applied to sponges; the solution is then wiped off with clean sponges.
5. The area surrounding the sterile field may be draped.
6. The skin overlying the puncture site is anesthetized using lidocaine, a 5-mL syringe, and a 25gauge needle. A 22-gauge needle is then substituted to anesthetize the underlying tissues.
7. With the stylet in place, the spinal needle is inserted at the midpoint of the chosen interspace. The needle should be parallel to the surface of the bed and angled slightly cephalad, or toward the umbilicus. The bevel of the needle should face upward, toward the face of the person performing the procedure.
8. The needle is advanced slowly until a pop, from penetration of the ligamentum flavum, is felt. The stylet is withdrawn to determine whether the CSF space has been entered, which is indicated by flow of CSF through the needle. If no CSF appears, the stylet is replaced and the needle advanced a short

distance; this is continued until CSF is obtained. If at some point the needle cannot be advanced, it is likely that bone has been encountered. The needle is withdrawn partway, maintained parallel to the surface of the bed, and advanced again at a slightly different angle.

9. When CSF is obtained, the stylet is reinserted. The patient is asked to straighten his or her legs, and the stopcock and manometer are attached to the needle. The stopcock is turned to allow CSF to enter the manometer to measure the opening pressure. The pressure should fluctuate with the phases of respiration.

10. The stopcock is turned to allow the CSF to be collected, and the appearance (clarity and color) of the fluid is noted. The amount obtained and the number of tubes required varies, depending on the tests to be performed. Typically, 1-2 mL are collected in each of five tubes for cell count, glucose and protein determination, VDRL, Gram's stain, and cultures. Additional specimens may be collected for other tests, such as oligoclonal bands and glutamine, and for cytologic study. If the CSF appears to contain blood, additional fluid should be obtained so that the cell count can be repeated on the specimen in the last tube collected. Cytologic studies, if desired, require at least 10 mL of CSF.

11. The stopcock and manometer are replaced to record a closing pressure.

12. The needle is withdrawn and an adhesive bandage is applied over the puncture site.

13. It has been customary to have the patient lie prone or supine for I or 2 hours after the procedure to reduce the risk of post-lumbar-puncture headache. Current evidence suggests this is unnecessary.

Complications

A. Unsuccessful Tap. A variety of conditions, including marked obesity, degenerative disease of the spine, previous spinal surgery, recent lumbar puncture, and dehydration, can make it difficult to perform lumbar puncture in the conventional manner. When puncture in the lateral decubitus position is impossible, the procedure should be attempted with the patient in a sitting position. If the tap is again unsuccessful, alternative methods include lumbar puncture by an oblique approach or guided by fluoroscopy; lateral cervical puncture; or cisternal puncture. These procedures should be undertaken by a neurologist, neurosurgeon, or neuroradiologist experienced in performing them.

B. Arterial or Venous Puncture. If the needle enters a blood vessel rather than the spinal subarachnoid space, it should be withdrawn and a new needle used to attempt the tap at a different level. Patients who have coagulopathy or are receiving aspirin or anticoagulants should be observed with particular care for signs of spinal cord compression from spinal subdural or epidural hematoma.

C. Post-lumbar-Puncture Headache. A mild headache, worse in the upright position but relieved by recumbency, is not uncommon following lumbar puncture and will resolve spontaneously over a period of hours to days. Frequency is directly related to the size of the spinal needle. Vigorous hydration or keeping the patient in bed for 1 or 2 hours after the procedure apparently does not reduce the likelihood of such headache. The headache usually responds to nonsteroidal anti-inflammatory drugs or caffeine. Severe and protracted headache can be treated by an autologous blood clot patch, which should be applied by experienced personnel.

Analysis of Results

A. Appearance. The clarity and color of the CSF should be observed as it leaves the spinal needle, and any changes in the appearance of fluid during the course of the procedure should be noted. CSF is normally clear and colorless. It may appear cloudy or turbid with white blood cell counts that exceed about 200/μL, but counts as low as about 50/μL can be detected by holding the tube up to direct sunlight and observing the light-scattering (Tyndall) effect of suspended cells. Color can be imparted to the CSF by hemoglobin (pink), bilirubin (yellow), or, rarely, melanin (black).

B. Pressure. With the patient in the lateral decubitus position, CSF pressure in the lumbar region does not normally exceed 180-200 mm water. When lumbar puncture is performed with patients in the sitting position, they should assume a lateral decubitus posture before CSF pressure is measured. Increased CSF pressure may result from obesity, agitation, or increased intra-abdominal pressure related to position; the latter factor may be eliminated by having the patient extend the legs and back once the CSF space has been entered and before the opening pressure is recorded. Pathologic conditions associated with increased CSF pressure include intracranial mass lesions, meningoencephalitis, subarachnoid hemorrhage, and pseudotumor cerebri.

C. Microscopic Examination. This may be performed either by the person who performed the lumbar puncture or by a technician at the clinical laboratory; it always includes a cell count and differential. Gram's stain for bacteria, acid-fast stain for mycobacteria, an India ink preparation for *Cryptococcus,* and cytologic examination for tumor cells may also be indicated. The CSF normally contains up to five mononuclear leukocytes (lymphocytes or monocytes) per microliter, no polymorphonuclear cells, and no erythrocytes. Erythrocytes may be present, however, if the lumbar puncture is traumatic (see below). Normal CSF is sterile, so that in the absence of central nervous system infection, no organisms should be observed with the various stains listed above.

D. Bloody CSF. If the lumbar puncture yields bloody CSF, it is crucial to distinguish between central nervous system hemorrhage and a traumatic tap. The fluid should be watched as it leaves the spinal needle to determine whether the

blood clears, which suggests a traumatic tap. This can be established with greater accuracy by comparing cell counts in the first and last tubes of CSF obtained; a marked decrease in the number of red cells supports a traumatic cause. The specimen should be centrifuged promptly and the supernatant examined. With a traumatic lumbar puncture, the supernatant is colorless. In contrast, following central nervous system hemorrhage, enzymatic degradation of hemoglobin to bilirubin in situ renders the supernatant yellow (xanthochromic). The time course of changes in CSF color following subarachnoid hemorrhage is outlined for bilirubin (yellow): appearance – 8-12 hours, maximum – 2-4 days, disappearance – 2-3 weeks.

Blood in the CSF following a traumatic lumbar puncture usually clears within 24 hours; blood is usually present after subarachnoid hemorrhage for at least 6 days. In addition, blood related to traumatic puncture does not clot, while clotting may occur with subarachnoid hemorrhage. Crenation (shriveling) of red blood cells, however, is of no diagnostic value.

In addition to breakdown of hemoglobin from red blood cells, other causes of CSF xanthochromia include jaundice with serum bilirubin levels above 4-6 mg/dL, CSF protein concentrations greater than 150 mg/dL, and, rarely, the presence of carotene pigments.

White blood cells seen in the CSF early after subarachnoid hemorrhage or with traumatic lumbar puncture result from leakage of circulating whole blood. If the hematocrit and peripheral white blood cell count are within normal limits, there is approximately one white blood cell for each 1000 red cells. If the peripheral white cell count is elevated, a proportionate increase in this ratio should be expected. In addition, every 1000 red cells present in CSF will increase the CSF protein concentration by about 1 mg/dL.