Unlike hypoxia-ischemia, which causes neuronal destruction, most metabolic disorders such as hypoglycemia, hyponatremia, hyperosmolarity, hypercapnia, hypercalcemia, and hepatic and renal failure cause only minor neuropathologic changes. The reversible effects of these conditions on the brain are not understood but may result from impaired energy supplies, changes in ion fluxes across neuronal membranes, and neurotransmitter abnormalities. For example, the high ammonia concentration of hepatic coma interferes with cerebral energy metabolism and with the Na^+, K^+-ATPase pump, increases the number and size of astrocytes, and causes increased concentrations of potentially toxic products of ammonia metabolism; it may also affect neurotransmitters, including the production of putative "false" neurotransmitters that are active at receptor sites. Apart from hyperammonemia, which of these mechanisms is of critical importance is not clear. The mechanism of the encephalopathy of renal failure is also not known. Unlike ammonia, urea does not produce central nervous system (CNS) toxicity, and a multifactorial causation has been proposed for the encephalopathy, including increased permeability of the blood-brain barrier to toxic substances such as organic acids and an increase in brain calcium and cerebrospinal fluid (CSF) phosphate content.

Coma and seizures are common accompaniments of large shifts in sodium and water balance in the brain. These changes in osmolarity arise from systemic medical disorders, including diabetic ketoacidosis, the nonketotic hyperosmolar state, and hyponatremia from any cause (e.g., water intoxication, excessive secretion of antidiuretic hormone, or atrial natriuretic peptides). Sodium levels <125 mmol/L induce confusion, and levels <115 mmol/L are typically associated with coma and convulsions. In hyperosmolar coma, the serum osmolarity is generally >350 mosmol/L. Hypercapnia depresses the level of consciousness in proportion to the rise in carbon dioxide (CO_2) tension in the blood. In all of these metabolic encephalopathies, the degree of neurologic change depends to a large extent on the rapidity with which the serum changes occur. The pathophysiology of other metabolic encephalopathies such as those due to hypercalcemia, hypothyroidism, vitamin B_{12} deficiency, and hypothermia are incompletely understood but must reflect derangements of CNS biochemistry, membrane function, or neurotransmitters.

Epileptic Coma Generalized electrical seizures are associated with coma, even in the absence of motor convulsions (nonconvulsive status epilepticus). The self-limited coma that follows a seizure, the postictal state, may be due to exhaustion of energy reserves or effects of locally toxic molecules that are the by-product of seizures. The postictal state produces continuous, generalized slowing of the background EEG activity similar to that of metabolic encephalopathies.

Toxic (Including Drug-Induced) Coma This common class of encephalopathy is in large measure reversible and leaves no residual damage provided there has not been cardiorespiratory failure. Many drugs and toxins are capable of depressing nervous system function. Some produce coma by affecting both the brainstem nuclei, including the RAS, and the cerebral cortex. The combination of cortical and brainstem signs, which occurs in certain drug overdoses, may lead to an incorrect diagnosis of structural brainstem disease. Overdose of medications that have atropinic actions produces signs such as dilated pupils, tachycardia, and dry skin; opiate overdose produces pinpoint pupils <1 mm in diameter.

Coma due to Widespread Damage to the Cerebral Hemispheres This category, comprising a number of unrelated disorders, results from widespread structural cerebral damage that simulates a metabolic disorder of the cortex. Hypoxia-ischemia is perhaps the best characterized and one in which it is not possible initially to distinguish the acute reversible effects of oxygen deprivation of the brain from the subsequent effects of anoxic neuronal damage. Similar widespread cerebral damage may be produced by disorders that occlude small blood vessels throughout the brain; examples include cerebral malaria, thrombotic thrombocytopenic purpura, and hyperviscosity. Diffuse white matter damage from cranial trauma or inflammatory demyelinating diseases can cause a similar coma syndrome.

APPROACH TO THE PATIENT: Coma

A video examination of the comatose patient is shown in Chap. 329e.

Acute respiratory and cardiovascular problems should be attended to prior to neurologic assessment. In most instances, a complete medical evaluation, except for vital signs, funduscopy, and examination for nuchal rigidity, may be deferred until the neurologic evaluation has established the severity and nature of coma. **The approach to the patient with coma from cranial trauma is discussed in Chap. 457e.**

HISTORY

The cause of coma may be immediately evident as in cases of trauma, cardiac arrest, or observed drug ingestion. In the remainder, certain points are useful: (1) the circumstances and rapidity with which neurologic symptoms developed; (2) the antecedent symptoms (confusion, weakness, headache, fever, seizures, dizziness, double vision, or vomiting); (3) the use of medications, drugs, or alcohol; and (4) chronic liver, kidney, lung, heart, or other medical disease. Direct interrogation of family, observers, and ambulance technicians on the scene, in person or by telephone, is an important part of the evaluation when possible.

GENERAL PHYSICAL EXAMINATION

Fever suggests a systemic infection, bacterial meningitis, encephalitis, heat stroke, neuroleptic malignant syndrome, malignant hyperthermia due to anesthetics, or anticholinergic drug intoxication. Only rarely is fever attributable to a lesion that has disturbed hypothalamic temperature-regulating centers ("central fever"). A slight elevation in temperature may follow vigorous convulsions. Hypothermia is observed with exposure that attends alcohol, barbiturate, sedative, or phenothiazine intoxication; hypoglycemia; peripheral circulatory failure; or extreme hypothyroidism. Hypothermia itself causes coma when the temperature is <31°C (87.8°F). Tachypnea may indicate systemic acidosis or pneumonia or, rarely, infiltration of the brain with lymphoma. Aberrant respiratory patterns that reflect brainstem disorders are discussed below. Marked hypertension suggests hypertensive encephalopathy or cerebral hemorrhage or head injury. Hypotension is characteristic of coma from alcohol or barbiturate intoxication, internal hemorrhage, myocardial infarction, sepsis, profound hypothyroidism, or Addisonian crisis. The funduscopic examination can detect subarachnoid hemorrhage (subhyaloid hemorrhages), hypertensive encephalopathy (exudates, hemorrhages, vessel-crossing changes, papilledema), and increased intracranial pressure (ICP) (papilledema). Cutaneous petechiae suggest thrombotic thrombocytopenic purpura, meningococcemia, or a bleeding diathesis associated with an intracerebral hemorrhage. Cyanosis and reddish or anemic skin coloration are other indications of an underlying systemic disease or carbon monoxide as responsible for the coma.

NEUROLOGIC EXAMINATION

The patient should be observed without intervention by the examiner. Tossing about in the bed, reaching up toward the face, crossing legs, yawning, swallowing, coughing, or moaning reflect a drowsy state that is close to normal awakeness. Lack of restless movements on one side or an outturned leg suggests a hemiplegia. Intermittent twitching movements of a foot, finger, or facial muscle may be the only sign of seizures. Multifocal myoclonus almost always indicates a metabolic disorder, particularly uremia, anoxia, drug intoxication (especially with lithium or haloperidol), or a prion disease (Chap. 453e). In a drowsy and confused patient, bilateral asterixis is a certain sign of metabolic encephalopathy or drug intoxication.

Decorticate rigidity and decerebrate rigidity, or "posturing," describe stereotyped arm and leg movements occurring spontaneously