Nelson Textbook of Paediatrics

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- Hyponatraemia
- Viral Meningoencephalitis
- SIADH
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ketoacidosis can increase plasma osmolality, shifting water from the ICF to ECF compartments. The reduced plasma sodium concentration caused by the influx of water into the extracellular fluid volume produces an invalid measure of plasma osmolality. In treating diabetic patients, it is essential to recognize the impact of the changes in plasma glucose concentration on ECF osmolality and on water shifts between the fluid compartments.

The second condition, which does not allow use of plasma sodium to estimate plasma osmolality, occurs with increases in serum solids. For example, when serum solids such as the proteins and lipids are increased, the water content in the serum is markedly decreased (expressed per liter of serum) because of volume displacement of water by lipids. Because electrolytes are dissolved in the aqueous phase of serum, electrolyte concentrations such as that of sodium determined by flame photometry and expressed as milliequivalents per liter of serum appear decreased even though the concentration per liter of serum water is normal. Treatment of such *pseudohyponatremia* is unnecessary and may be detrimental to the patient. Its occurrence can be recognized by measuring serum osmolality by freezing point depression, a method that measures solute concentration of the water fraction of serum and more accurately reflects serum sodium concentration. The problem of pseudohyponatremia is avoided by methods measuring sodium concentration with ion-specific electrodes.

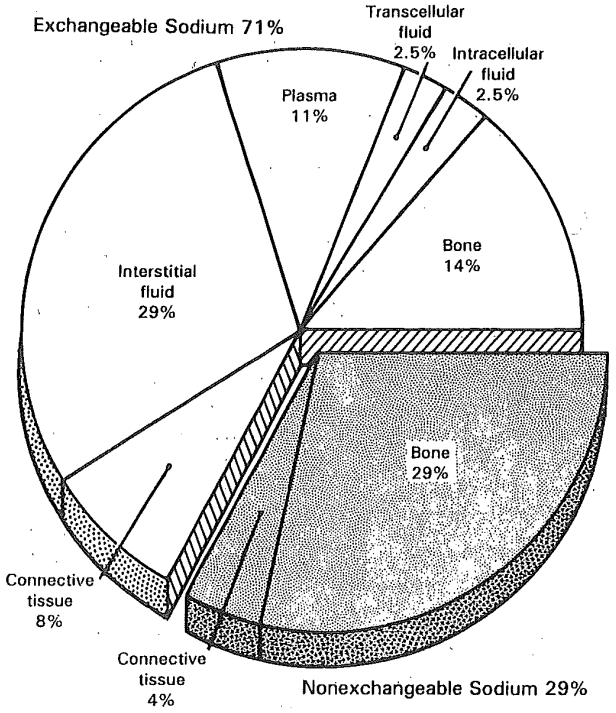


Figure 47–1. Distribution of body sodium as a percentage of the total. Exchangable sodium *(clear)* and nonexchangeable sodium *(stippled)* are indicated. (From Frohnert PP: Body composition. *In*: Knox FG (ed): Textbook of Renal Pathophysiology. Hagerstown, MD, Harper & Row, 1978.)

# Chapter 47
# *Sodium*

**BODY CONTENT AND DISTRIBUTION OF SODIUM.** Sodium, the bulk cation of the extracellular fluids, is the principal osmotically active solute responsible for the maintenance of intravascular and interstitial volumes. Of the total quantity of sodium in the body, more than 30% is nonexchangeable or only slowly exchangeable, bound in poorly mobilizable tissues (Fig. 47–1). Of total body sodium, 11% is in the plasma sodium pool, 29% is in the interstitial lymph fluid, and 2.5% is in the intracellular fluid. About 43% of total body sodium is in bone, but only one third of the sodium in bone is exchangeable. Dense connective tissue and cartilage contains 12% of body sodium, of which about two thirds is exchangeable (see Fig. 47–1). The *exchangeable sodium content of the fetus* averages 85 mEq/kg, compared with the adult value of 40 mEq/kg, because the fetus has relatively large amounts of cartilage, connective tissue, and extracellular fluid, all of which contain considerable amounts of sodium, and has a relatively small mass of muscle cells, which have a low sodium content.

Although cell membranes are relatively permeable to it, sodium is predominantly distributed in the extracellular compartment. Intracellular concentrations are maintained at levels of approximately 10 mEq/L and extracellular concentrations of approximately 140 mEq/L. The low intracellular concentration is achieved by active extrusion of sodium from cells by the sodium-potassium–activated and magnesium-activated ATPase systems. Calcium inhibits ATPase, as do ouabain and related cardiac glycosides.

Although intracellular concentrations of sodium are low and represent a small part of total body sodium, they may be critical in modifying certain intracellular enzyme activities. The intracellular sodium content usually remains relatively constant, and changes in total body sodium reflect mostly changes in extracellular sodium. However, redistribution of sodium between the intracellular and extracellular compartments may occur in the absence of significant changes in total body sodium. Such a change (e.g., increased intracellular sodium) may be observed in the severely ill patient, in whom it usually is referred to as the "sick cell syndrome." Intracellular sodium may also be increased in some forms of hypertension.

Because of the Donnan distribution of anionic proteins, the concentration of sodium in interstitial fluid is approximately 97% of that of the serum sodium value; changes in concentration of sodium in the serum are reflected by proportional changes in the concentration of sodium in the interstitial fluid. Concentrations of sodium in transcellular fluids vary considerably because such fluids are not in simple diffusion equilibrium with plasma. Unexpected changes in the composition of these fluids may occur and may necessitate changing the therapeutic regimens designed to replace their abnormal loss.

**REGULATION OF SODIUM. Intake.** The amount of sodium in the body is determined by the balance between intake and excretion. Compared with the thirst mechanism for water, the regulatory mechanism of sodium *intake* is poorly developed but may respond to large changes; for example, salt craving may occur in some patients with salt-wasting syndromes. However, sodium intake normally depends on cultural customs. In the United States, the average adult usually takes in about 170 mEq/24 hr, equivalent to 10 g of salt. Children take in less, proportionate to their smaller food intake, but still well in excess of maintenance needs. Infants generally have a relatively high sodium intake because of the high sodium content of cow's milk (21 mEq/L). The sodium content of many infant formulas is also high compared with breast milk (7 mEq/L). The sodium dietary intake of older children and adolescents varies but usually is relatively high because of ingestion of fast foods and junk foods.

**Absorption.** Occurring throughout the gastrointestinal tract, minimally in the stomach and maximally in the jejunum, absorption probably takes place by way of a sodium-potassium–activated adenosine triphosphatase (ATPase) system, which facilitates the movement of sodium by a transport protein that couples sodium with glucose. The intestinal transport mechanism of sodium is augmented by aldosterone or desoxycorticosterone acetate.

**Excretion.** Sodium excretion occurs through urine, sweat, and feces. The kidney is the principal organ for the facultative regulation of sodium output. Normally, the concentration of sodium in sweat ranges from 5 to 40 mEq/L. Higher values are seen in cystic fibrosis, which may contribute to body loss of sodium, and Addison disease, and lower values are observed in sodium depletion and hyperaldosteronism. There is little evidence that changes in the level of sodium in sweat are part of the excretory mechanism for regulating the sodium content of the body under normal circumstances. In the absence of diarrhea, fecal concentrations of sodium are low.

**Renal Regulation of Sodium Excretion.** Renal regulation of sodium depends on a balance between glomerular filtration and tubular reabsorption. Normally, the amount of sodium filtered daily by the kidneys is more than 100 times that ingested and more than five times the total amount of sodium in the body. However, of the total amount of sodium filtered by the kidneys each day (25,200 mEq/24 hr), less than 1% or 50 mEq/24 hr, is excreted in the urine; the remaining 99% is reabsorbed along the length of the renal tubule, representing the result of a highly efficient regulatory process.

*Glomerular Filtration of Sodium.* Under normal conditions, changes in glomerular filtration rate (GFR) do not affect sodium homeostasis. A constant fraction of the filtered load of sodium is reabsorbed in the proximal tubule despite transient, spontaneous variations in the GFR. This balance of filtration and reabsorption, called glomerular-tubular balance, reduces the impact of spontaneous changes in GFR on the amount of renal sodium excretion. Moreover, sodium balance can be achieved when the GFR remains stable even though sodium intake varies. However, the GFR may play a role in sodium excretion during conditions that also stimulate sodium regulatory mechanisms through changes in extracellular volume. The factors that affect the GFR and promote sodium reabsorption in response to a decrease in extracellular volume, such as hemorrhage or dehydration, are activation of sympathetic renal nervous system and stimulation of the renin-angiotensin system. When extracellular volume expansion occurs, atrial natriuretic peptide (ANP) is released into the circulation from the cardiac atria and causes increased urinary losses of sodium, in part as a response to increased GFR.

*Tubular Reabsorption of Sodium.* The integrated action of all the nephron segments results in the regulation of renal sodium excretion (Fig. 47–2). Renal sodium handling is characterized by two coordinated tubular processes. First, reabsorption of sodium in the proximal tubule and loop of Henle delivers a constant proportion of the filtered load of sodium to the distal nephron. Second, reabsorption of sodium in the distal tubule and collecting duct is the fine regulator of the final amount of sodium excreted, which closely matches the amount of sodium ingested. Under normal circumstances, approximately two thirds of the filtered sodium is reabsorbed by the proximal convoluted tubule (see Fig. 47–2).

Because the percentages of filtered sodium and water reabsorbed in the proximal tubule are proportional, the fluid remaining at the end of the proximal convoluted tubule has a sodium concentration comparable to that in the plasma. Net movement of sodium out of the proximal tubule represents the balance between sodium reabsorbed from the luminal fluid (i.e., transcellular and paracellular) and that returned through

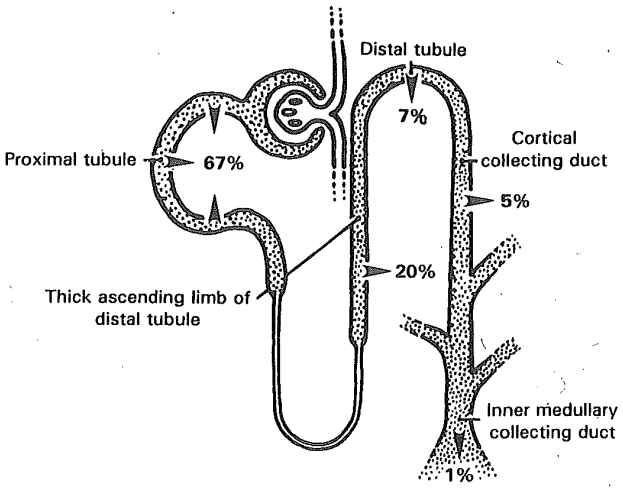


Figure 47–2. Segmental sodium reabsorption along the nephron as a percentage of the filtered load of sodium. (From Koeppen BM, Stanton BA: Renal Physiology. St. Louis, Mosby Year Book, 1992.)

intercellular spaces. The movement of transcellularly reabsorbed sodium across the proximal tubule cell membrane is coupled with the reabsorption of organic solutes and anions, such as glucose and chloride, and facilitated by specific membrane transport proteins. Reabsorbed sodium is actively transported out of the cells across their basolateral membranes, producing an osmotic gradient that causes the movement of an equivalent amount of water. The resulting hydrostatic force in the intercellular spaces and interstitial fluid, as well as the exertion of oncotic pressure by the plasma protein in the peritubular capillary, is responsible for returning the reabsorbed sodium and water into the peritubular capillary and, ultimately, into the systemic circulation.

Significant sodium reabsorption (approximately 20%) occurs in the *loop of Henle* (see Fig. 47–2) and is central to the countercurrent multiplier system essential for water balance and the concentration of urine. Water reabsorption occurs in the descending limb of the loop of Henle, and sodium reabsorption occurs in the ascending limb. Sodium transport at the thick ascending limb is active, and it may be secondary to the active transport of chloride rather than primary, as it is at most other sites. Although the loop of Henle is important in the overall control of sodium reabsorption, no precise regulating mechanism has been delineated, nor has a maximal rate for sodium transport at this site been demonstrated. When the load of sodium delivered to the loop is increased by changes in the GFR or in sodium reabsorption in the proximal tubule, most of the excess load is reabsorbed in the loop, providing a further protective mechanism and limiting the magnitude of changes of sodium delivery to the distal convoluted tubule.

The fine regulation of sodium balance probably occurs throughout the distal nephron in the *distal convoluted tubules* and the *collecting ducts*. The distal convoluted tubule reabsorbs 7% and the collecting duct 5% of the filtered load of sodium (see Fig. 47–2). With the proximal tubule and loop of Henle reabsorption of sodium producing a regulated, proportioned delivery of sodium to these sections of the nephron, only small adjustments in distal convoluted tubule and collecting duct reabsorption are required to balance urinary sodium excretion with intake to maintain homeostasis.

Sodium reabsorption at these sites is regulated by aldosterone, whose secretion is governed by the renin-angiotensin system and, to some degree, by potassium balance (Fig. 47–3).

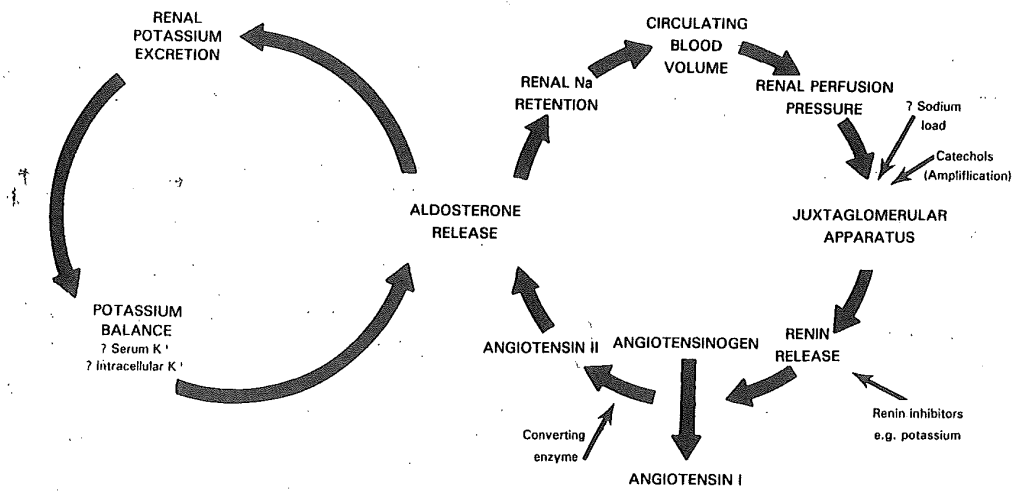


Figure 47–3. Correlations of the volume and potassium feedback loops with aldosterone secretion. Integration of the signals from each loop determines the level of aldosterone secretion. (From Williams GH, Dluhy RG: Aldosterone biosynthesis: interrelationship of regulating factors. Am J Med 53:595, 1972.)

Throughout the distal tubule and collecting duct, sodium is reabsorbed against a large concentration gradient from lumen to plasma. However, compared with the proximal convoluted tubule and the loop of Henle, the total capacity for sodium reabsorption is more limited. If the load of sodium reaching the distal tubule increases significantly, reabsorption does not increase proportionately, and the added load is excreted in the urine.

In health, less than 1% of filtered sodium is normally excreted in the urine. However, to maintain sodium balance, this amount may increase to 10% or higher in response to a high sodium intake and can decrease to very low levels in response to reduced dietary sodium. The considerable flexibility prevents a significantly positive or negative sodium balance when dietary sodium intake fluctuates. However, it takes about 3 days for a new steady state to be achieved after the dietary intake of sodium has been markedly altered.

**FACTORS REGULATING SODIUM EXCRETION.** An important factor regulating the renal handling of sodium is the *renin-angiotensin system* (see Fig. 47–3). The proteolytic enzyme renin is released from the juxtaglomerular apparatus, which is anatomically composed of the specialized cells in the afferent arteriole and in the segment of the distal tubule that contacts the glomerular vascular pole, the macula densa. Stimuli for the release of renin include decreases in renal perfusion pressure detected in the afferent arteriole and a decrease in sodium chloride concentration or delivery to the macula densa.

Angiotensin I is formed by cleavage of the substrate angiotensinogen by renin. Angiotensin I is converted to angiotensin II by a specific converting enzyme. Angiotensin II, by inhibiting renin secretion, acts as a negative-feedback regulator of renin release. The renin-angiotensin system regulates tubular sodium reabsorption by the direct stimulation of sodium reabsorption in the proximal tubule by angiotensin II and by the stimulation of *aldosterone* secretion by angiotensin II. Aldosterone, a mineralocorticoid produced in the adrenal gland, is an important promoter of sodium reabsorption in the late distal convoluted tubule and collecting duct. While increasing sodium reabsorption, aldosterone also increases potassium secretion and the loss of potassium in the urine. In general, activation of the renin-angiotensin system enhances tubular reabsorption of sodium and results in decreased urinary sodium excretion. Under conditions of extracellular volume expansion or plasma sodium excess, the renin-angiotensin system is suppressed and urinary sodium excretion is increased.

*Atrial natriuretic peptide (ANP)* is a potent natriuretic and diuretic peptide hormone produced and stored in the atrial myocytes. The target organ of ANP is the kidney, in which it increases sodium and water excretion. ANP is released into the circulation from its cardiac location in response to expansion of the extracellular fluid volume and the resulting stretch of the cardiac atria. The urinary sodium and water excretory actions of ANP generally antagonize the sodium-retaining mechanisms of the renin-angiotensin system. ANP is an important regulator of acute or short-term changes in extracellular fluid volume. However, the role for ANP as a long-term regulator of sodium homeostasis is less certain.

*Starling forces* in the intercellular space of the proximal tubule cells and the interstitial space between the tubular cells and the peritubular capillaries influence the movement of reabsorbed solute and water into the peritubular capillaries. Normally, the sum of Starling forces favors the movement of solute and water from the intercellular and interstitial spaces into the peritubular capillary. Reabsorbed solute and water are returned to the tubular lumen through paracellular pathways when the normal balance of these forces is altered. Rapid expansion of the extracellular fluid volume increases the interstitial hydrostatic pressure, preventing sodium reabsorption and producing increased urinary sodium excretion.

**PATHOPHYSIOLOGIC CONDITIONS.** Pathophysiologic changes in serum sodium concentration in the absence of serum solids excess, such as hyperlipidemia or hyperglycemia, usually result from changes in body water, sodium, or a combination of the two. The serum sodium concentration does not necessarily reflect the status of total body sodium content, as previously described. A particular abnormality of serum sodium concentration must be understood in the context of sodium and water regulation.

**Hypernatremia.** Hypernatremia (serum sodium >150 mEq/L) is caused by conditions that produce an excessive gain of sodium or result in an excessive loss of body water that is greater than the loss of sodium. Hypernatremia due to an excessive gain of sodium, primary sodium excess (Table 47–1), is usually associated with iatrogenic causes: the substitution of NaCl for glucose in infant formulas prepared on site from basic ingredients, the overuse of saline enemas, inappropriate intravenous adminis-

■ TABLE 47–1 Pediatric Causes of Hypernatremia

| |
|---|
| **Primary Sodium Excess** |
| Improperly mixed formula or rehydration solution |
| Accidental substitution of NaCl for glucose in infant formulas |
| Excessive sodium bicarbonate during resuscitation |
| Hypernatremic enemas |
| Ingestion of sea water |
| Hypertonic saline intravenous administration |
| NaCl used to induce vomiting |
| Intentional salt poisoning (i.e., Münchausen by proxy) |
| High breast milk sodium |
| **Primary Water Deficit** |
| Diabetes insipidus |
| Central |
| Nephrogenic |
| Diabetes mellitus or other solute diuresis |
| Gastroenteritis (i.e., water loss greater than solute loss) |
| Inadequate breast feeding |
| Intentional withholding of water intake |
| Increased insensible water loss (e.g., premature infant) |
| Adipsia |
| Inadequate access to free water |

tration of hypertonic saline solutions, and NaCl used to induce vomiting. The more commonly encountered causes of hypernatremia are those caused by a primary water deficit (see Table 47–1), in which the loss of total body water exceeds any loss of sodium.

Diabetes insipidus (see Chapter 46) is caused by one of two fundamental defects in renal water regulation. *Central diabetes insipidus* is caused by a defect in the release of antidiuretic hormone (ADH) into the circulation. The abnormality in central diabetes insipidus can occur in the production, transport, storage, or release of ADH. Any condition, such as trauma, neoplasms, or congenital central nervous system defects, that disrupts the osmoreceptor-hypothalamus-hypophyseal axis results in defective ADH release and excessive urinary water loss. *Nephrogenic diabetes insipidus* is a sex-linked recessive disorder caused by a defective ADH receptor on the tubular cell membrane. The release of ADH in these patients is normal, but the tubular cell is not able to respond to ADH. This condition is present at birth, and if unrecognized, it can be life threatening or result in serious complications. Repeated episodes of extreme hypernatremia may produce permanent central nervous system damage.

*Gastroenteritis*, usually predominately diarrhea that causes large amounts of stool water loss that is greater than the amount of solute lost, is the most common cause of hypernatremia in childhood.

*Inadequate breast feeding* must be considered in a newborn with hypernatremia. In most of these cases, the breast milk sodium concentration is not elevated, but there have been case reports of hypernatremia associated with elevated breast milk sodium concentration. In an otherwise normal infant, decreased water intake from an inadequate breast milk supply cannot match the obligatory water losses, and hypernatremia ensues.

*Withholding of water intake* may produce hypernatremia if the water intake is withheld to such a degree that it is exceeded by obligatory water losses. Two groups of children are vulnerable to developing this type of hypernatremia: neurologically compromised individuals who cannot express thirst or obtain water and severely abused children. Lack of access to water occurs in children who, because of age or a handicapping condition, cannot provide themselves with water intake.

**Hyponatremia.** Hyponatremia (serum sodium <130 mEq/L) is caused by conditions that create primary sodium deficits resulting in the depletion of sodium; produce a gain in total body water; combine sodium and water abnormalities (Table 47–2).

Primary sodium deficits involve a disruption in renal sodium handling. *Renal sodium losses* occur in conditions with intrinsic renal defects in sodium regulation. Premature infants can lose sodium in the urine because of the immaturity of the sodium reabsorptive capacity. *Renal salt wasting* due to congenital urinary tract anomalies, obstruction, hypoplasia, dysplasia, or other congenital renal diseases, such as medullary sponge kidney, produce significant urinary sodium losses despite a low serum sodium. Adrenal insufficiency resulting in *mineralocorticoid deficiency* is most commonly seen in children with congenital adrenal hyperplasia. Renal losses of sodium also occur during the recovery phase of acute tubular necrosis with the chronic use of diuretics and resulting from the osmotic diuresis that accompanies diabetes mellitus.

Extrarenal losses of sodium often accompany gastrointestinal fluid losses through unreplaced nasogastric fluid losses or gastroenteritis. This type of gastroenteritis, associated with intestinal water losses and significant sodium losses, usually includes vomiting and diarrhea. The hyponatremia produced by the greater loss of sodium than water is exacerbated by the intake of low-solute beverages.

The most common cause of hyponatremia due to decreased *nutritional* sodium intake is the WIC syndrome. This form of water intoxication is seen in small infants who receive large amounts of very-low-sodium–containing fluids, usually to the exclusion of normally concentrated formulas. These infants present with profound hyponatremia and serious central nervous system symptoms, such as seizures.

Of the disorders resulting in a primary water excess, the most common is the *syndrome of inappropriate ADH secretion (SIADH)*. This disorder, which has many potential causes, is marked by the secretion of ADH in the absence of a physiologic stimulus for its secretion. The increased ADH secretion increases collecting duct water reabsorption and dilutes the extracellular fluid, producing hyponatremia. In children, of the many conditions associated with SIADH, the most common occurs as a complication of acute meningitis.

The hyponatremia of water excess involves the addition of

■ TABLE 47–2 Pediatric Causes of Hyponatremia

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|---|
| **Sodium Deficit with Sodium Depletion** |
| ***Renal Losses*** |
| Prematurity |
| Acute tubular necrosis, recovery phase |
| Diuretics |
| Renal salt wasting |
| Mineralocorticoid deficiency |
| Expanded extracellular fluid |
| Osmotic diuresis |
| Renal tubular acidosis |
| ***Extrarenal Losses*** |
| Vomiting and diarrhea |
| Third spacing |
| Burns |
| Nasogastric drainage |
| Cystic fibrosis |
| Excess sweating |
| ***Nutritional Deficits*** |
| WIC syndrome (i.e., inadequate oral sodium intake) |
| Inadequate sodium in parenteral fluids |
| Cerebrospinal fluid drainage |
| Burns |
| Paracentesis |
| **Water Excess with Water Gain** |
| Syndrome of inappropriate antidiuretic hormone secretion |
| Glucocorticoid deficiency |
| Hypothyroidism |
| Drugs |
| Excess parenteral fluid administration |
| Psychogenic polydipsia |
| Tap water enemas |
| **Excess of Sodium and Water** |
| Nephrotic syndrome |
| Cirrhosis |
| Cardiac failure |
| Acute and chronic renal failure |

excess water from an exogenous source, such as the use of dilute or sodium-poor intravenous fluids for the treatment of dehydration. Conditions producing hyponatremia combining abnormal retention of sodium and water usually involve the edema-forming diseases of *nephrotic syndrome and cirrhosis*. In these conditions, water shifts from plasma to the interstitial spaces, which stimulates thirst and releases ADH, causing water and sodium retention. The resulting water retention is greater than the sodium retention, producing hyponatremia. *Cardiac failure* activates similar water- and sodium-retaining mechanisms, but the plasma oncotic pressure remains normal.

# Chapter 48
# Potassium

**BODY CONTENT AND DISTRIBUTION OF POTASSIUM.** The body content of potassium, the major intracellular cation, correlates well with the lean body mass. Because potassium is predominantly intracellular (see Fig. 46–3), the change in body potassium content that occurs with growth is an excellent index of cellular mass at different ages. In the adult, 90% of total body potassium is exchangeable. The exchangeable components are intracellular potassium (89.6%) and extracellular potassium: plasma (0.4%) and interstitial lymph (1.0%). The remainder (10%) of total body potassium is nonexchangeable and is contained in dense connective tissue and cartilage (0.4%), bone (7.6%) and as a small amount of intracellular potassium (2%).

Intracellular concentrations of potassium approximate 150 mEq/L of cell water. The extracellular concentration of potassium (4 mEq/L) creates a large concentration difference across the cell membranes. The difference between intracellular and extracellular potassium, sustained by the action of Na, K-ATPase, is important for maintaining the resting membrane potential difference across the cell membrane. Potassium is critical for the excitability of nerve and muscle cells and for the contractility of cardiac, skeletal, and smooth muscle. Because of its intracellular osmotic contribution, potassium is also important for the maintenance of cell volume.

**REGULATION OF POTASSIUM.** Potassium exists in remarkably constant quantities in almost all animal and vegetable tissues. A daily intake of 1–2 mEq/kg body weight is recommended, but intakes vary widely. Absorption of potassium is reasonably complete in the upper gastrointestinal tract. More distally, body potassium is exchanged for sodium in the lumen of the lower bowel.

Two sets of mechanisms participate in potassium homeostasis. These mechanisms maintain an intracellular potassium concentration differential and match potassium dietary intake, mainly through regulating renal potassium excretion. Acute potassium loads require well-developed extrarenal mechanisms to prevent severe hyperkalemia and to avoid potassium toxicity. In the first 4–6 hr after a potassium load, only one half of the potassium is excreted by the kidneys. Some potassium is secreted into the intestinal tract. More than 40% is translocated into cells, primarily in the liver and muscle. This process is an important protective mechanism and is regulated by insulin and epinephrine, which enhance potassium uptake. The catecholamine effect appears to be mediated through β-receptors. Stimulation of α-adrenergic receptors impairs extrarenal disposal of an acute potassium load.

Aldosterone plays a key role in the renal and extrarenal handling of potassium. Its primary extrarenal site of action may be the gastrointestinal tract, although it also affects muscle transport of potassium. Glucocorticoids may also be important in extrarenal potassium homeostasis. Glucagon infusion causes a transient hyperkalemia, but its role in potassium regulation is not clear.

The acid-base balance affects intracellular shifts of potassium. Systemic acidosis results in the movement of potassium out of cells; alkalosis produces the opposite effect. For every 0.1 unit change in blood pH, the plasma potassium concentration changes 0.3–1.3 mEq/L in the opposite direction. The changes depend on numerous factors. For example, the increase in serum potassium accompanying respiratory acidosis is much less than that with metabolic acidosis.

Chronic potassium balance is primarily regulated by the kidneys, which can adjust the amount of potassium excreted over a wide range. Normally, the rate of potassium excretion in the urine approximates 10–15% of that filtered. With the administration of large amounts of potassium, urinary excretion may be more than twice the amount filtered at the glomerulus. Conversely, urinary concentrations can be reduced to very low levels if potassium conservation is required. In the adult, rates of urinary potassium excretion may range from less than 5 mEq to 1,000 mEq/24 hr, depending on the amount of potassium intake.

Potassium is freely filtered in the glomerulus. Its concentration along the length of the proximal convoluted tubule is similar to that of plasma, indicating that reabsorption of potassium in this segment of the nephron is proportionate to that of water, with 60% or more of the filtered potassium absorbed. Concentrations of potassium are increased in the loop of Henle. However, by the time tubular fluid reaches the early distal convoluted tubule, its potassium concentration is below that of plasma, and the amount of potassium delivered to more distal segments of the nephron is less than 10% of the filtered load. The distal tubule and collecting duct have the dual capabilities of potassium reabsorption and secretion.

Under conditions of maximal potassium conservation, continued reabsorption occurs in the distal tubule; when dietary intake is normal or when excretion is increased for other reasons, potassium secretion takes place in the distal tubule and possibly in the collecting duct. The primary mechanism regulating renal control of potassium homeostasis is potassium secretion in these segments of the nephron. The cellular mechanisms of potassium secretion in the distal nephron are regulated by several clinically relevant factors. Increases in plasma potassium stimulate the tubular cell secretion of potassium, and decreases of plasma potassium inhibit tubular secretion.

Aldosterone promotes potassium secretion in the tubule through a series of intracellular events in the tubular cell, including increased luminal membrane permeability to potassium. Aldosterone secretion is stimulated by increased plasma potassium and angiotensin II (see Fig. 47–3). Atrial natriuretic peptide (ANP) and low plasma potassium inhibit aldosterone secretion. Increased tubular flow rate through the potassium-secreting nephron segments due to diuretics or extracellular volume expansion stimulates potassium secretion.

Acid-base status, which affects the cellular potassium concentration, also regulates tubular potassium handling. Alkalosis stimulates and acidosis inhibits secretion. A rise of tubular fluid sodium concentration, such as that produced by diuretics, stimulates potassium secretion. Diuretics can promote renal potassium secretion and urinary potassium loss by increasing tubular fluid flow rate and by increasing tubular sodium concentration. Most of the potassium in the final urine probably results from tubular secretion rather than glomerular filtration.

Potassium is also lost in the feces and in sweat. The exchange of plasma potassium for sodium in the colonic contents contributes to sodium conservation and permits the colon to partici-

given early if the urine output is good. Clinical and electrocardiographic improvement may be more rapid with magnesium therapy, and seizures occurring during recovery from diarrhea complicating severe malnutrition may respond to magnesium.

## 56.3† Congenital Alkalosis of Gastrointestinal Origin

Rarely, chronic diarrhea may result from a congenital defect in the transport of chloride in the small and large bowels. The watery stools of these patients have a high content of chloride and alkalosis results from the ensuing volume depletion. Potassium is lost in the stools and in the urine; the latter losses are a consequence of the alkalosis. Treatment of fluid and electrolyte deficits is similar to that for pyloric stenosis. Long-term therapy must provide an adequate dietary intake of potassium and chloride. A rare, acute, chloride-losing diarrhea may also occur.

## 56.4 Pyloric Stenosis

(Also see Chapter 275.1)

This condition exemplifies the correction of deficits associated with alkalosis. The therapy differs little from that for other causes of dehydration, except that potassium replacement should begin early, as soon as the child has urinated. In addition, relatively more sodium and potassium should be given as the chloride salt than is usual in treating dehydration, partly because of the larger deficit of chloride in pyloric stenosis and partly because this results in some correction of the alkalosis as the volume is expanded. Correction of the hypochloremia and alkalosis by administering ammonium chloride without correcting the potassium deficit is not recommended because it results in continued dysfunction of renal tubular and other cells.

Severe depletion of intracellular potassium results in the increased exchange of hydrogen ion for sodium in the distal tubules of the kidney. The paradoxical presence of an acid urine with systemic alkalosis should be interpreted as signifying a marked potassium deficit and a need to increase the amount of potassium used for repletion.

It is not uncommon for deficits to be replaced and serum levels of electrolytes returned to normal within 12 hr. However, except in the mildly ill infant without signs of dehydration, it is preferable to delay surgery for at least 36–48 hr to achieve optimal readjustment of body functions. During this preparation period, adequate fluid therapy prevents dehydration, and the stomach may be decompressed by gentle suction.

## 56.5 Fasting and Thirsting

Parenteral fluid therapy is usually required in initially treating the infant or child who has taken little or no water and food for 1–5 days. Such infants are deficient in water from insensible water loss and in electrolytes, particularly sodium and chloride, which have been excreted in the urine. If fasting and thirsting continue beyond 4–5 days, urinary output falls to such low levels that there is reduced continued loss of electrolytes. Further severe water deficiency associated with continued evaporative losses may result in hypernatremia.

Therapy is begun with an isotonic solution to produce rapid and safe expansion of extracellular volume and to improve renal function. Subsequent therapy is described in Chapter 55. Sodium and water depletion per kilogram of body weight for a given degree of clinical dehydration is generally greater in infants than in children, but potassium deficits are relatively equal in infants, children, and adults. Water, carbohydrate, and electrolytes may be administered orally to the mildly ill patient. Because infants may vomit when they are dehydrated, they may require parenteral therapy.

For a detailed discussion of the fluid therapy of children with diabetic ketoacidosis and burns, see Part XXVI, Section 6 and Chapter 60.

## 56.6 Electrolyte Disturbances Associated with Central Nervous System Disorders

Diseases of the central nervous system are frequently associated with disturbances in sodium concentration. Patients with diverse lesions, such as surgical or traumatic damage to the brain, encephalitis, brain abscess, brain tumors, Guillain-Barré syndrome, bulbar poliomyelitis, cerebrovascular accidents, tumors of the fourth ventricle, subdural hematomas, and meningitis, may present with hyponatremia. Most hyponatremia in this setting is associated with normal total body sodium, with minimal or no negative sodium balance. A decrease in serum sodium is almost entirely the result of retention of water.

The diagnosis of a *syndrome of inappropriate antidiuretic hormone* (SIADH) is considered in the absence of hypovolemia, edema, endocrine dysfunction (including primary and secondary adrenal insufficiency and hypothyroidism), renal failure, and drugs impairing water excretion. Along with central nervous system disorders such as those mentioned and neonatal hypoxia or hydrocephalus, this syndrome is also found in patients with pulmonary disorders, including pneumonia, tuberculosis, and asthma; those on positive-pressure ventilation; and in those with certain carcinomas. The diagnosis is established by measuring inappropriate secretion of ADH under hypotonic conditions and represents a defect in osmoregulation of vasopressin. Patients with this syndrome generally have a concentrated urine despite the presence of hyponatremia and a urinary sodium concentration greater than 20 mEq/L.

Treatment of acute symptomatic hyponatremia should be prompt and use hypertonic saline in combination with furosemide to enhance free water excretion. Chronic, asymptomatic hyponatremia is best managed conservatively by water restriction to allow a gradual increase of serum sodium over 24–48 hr. Occasionally, an individual with a central nervous system lesion has hyponatremia associated with true salt wasting. In this situation, there are signs of volume depletion, including weight loss, signs of dehydration, hypotension, and a diminished GFR with azotemia. This situation requires the appropriate administration of salt to restore volume status.

## 56.7 Perioperative Fluids

Preoperatively, preparing a patient having no pre-existing deficit or in whom the deficit has been repaired consists mainly

of supplying adequate carbohydrate for sustenance and sparing of protein breakdown. The usual maintenance requirements of water and electrolytes are appropriate. Young infants who are not vomiting should receive carbohydrate and sodium chloride mixtures by mouth until 3 hr before the operation. Such fluids are readily absorbed from the gastrointestinal tract. Preparing the newborn involves certain unique hazards. Deficits of water and electrolytes from vomiting or from stasis caused by intestinal obstruction should be replaced before operating. In cases of intestinal obstruction, conjugated bilirubin may be deglucuronidated by intestinal enzymes; enterohepatic circulation of unconjugated bilirubin can then lead to high serum levels and kernicterus. Hypoprothrombinemia also should be prevented by administering 1 mg of vitamin $K_1$ oxide.

During surgery, blood, plasma, saline, or other volume expanders may be given if blood loss, tissue trauma, third spacing, or excessive evaporative loss occurs. The magnitude of such losses is best judged by the experienced surgeon as he or she operates. *The most common error in administering parenteral fluid during and after surgery is excessive administration,* particularly of dextrose in water. Under most circumstances, little to no potassium need be administered during this time, because extensive tissue trauma or anoxia may result in the release of large amounts of intracellular potassium, with the potential of causing hyperkalemia. If shock occurs, acute renal failure may ensue, impairing the ability to eliminate through the renal route large amounts of released potassium.

Postoperatively, intake should be limited for 24 hr. Thereafter, the usual maintenance therapy is gradually resumed. The water intake should not exceed 85 mL/100 kcal metabolized because of antidiuresis resulting from trauma, circulatory readjustment, or anesthesia unless renal ability to concentrate the urine is limited, as in patients with sickle cell disease, chronic pyelonephritis, or obstructive uropathy. If the intake of water is not limited, whether given parenterally or orally, water intoxication may occur. Maintenance sodium intake may also be low because of the low caloric expenditure during anesthesia and postoperatively. Fluid therapy in the postoperative period largely depends on the complex but anticipated response of the body to trauma through modification of water and sodium excretion and the concomitant occurrence of common or unanticipated complications from surgery. The patient's clinical condition dictates the final fluid and electrolyte requirements that occur as a net effect of these processes.

Some postoperative children have elevated blood ADH levels due to SIADH or to an appropriate response to fluid restriction and resultant volume contraction. If decreasing urine output after surgery is the result of SIADH, the patient is euvolemic, has a normal circulatory status, has stable to slightly increased weight, and has an elevated urinary sodium excretion. If a child has oliguria related to third spacing and true depletion of intravascular volume, there is decreased urinary sodium excretion associated with clinical signs of hypovolemia, such as weight loss, tachycardia, changes in skin turgor and peripheral perfusion, and hypotension.

## 56.8 Isolated Disturbances in Blood pH and Concentrations of Electrolytes

**ACIDOSIS.** *Respiratory acidosis,* in which the pH may be markedly lowered, primarily as a result of retention of carbon dioxide, may be seen with severe respiratory insufficiency, with respiratory distress syndrome in the newborn infant, and in patients receiving assisted ventilation for any reason who may be inadequately ventilated or have airway blockage. Acute respiratory acidosis may also be a manifestation of child abuse and be associated with strangulation. Mild metabolic acidosis may coexist because hypoxia leads to the accumulation of lactic and other organic acids in the extracellular fluid (see chapter 53).

Measurements of blood pH and gases should guide the correction of acidosis. The appropriate treatment is to improve ventilation by assisting respiration rather than by administering sodium bicarbonate, which may produce hyperosmolality and cardiac failure.

*Metabolic acidosis,* which can result from renal tubular acidosis, renal insufficiency, or from accumulation of organic acids, may require the administration of alkali, especially if symptoms are evident. In lactic acidosis, in glycogen disorders, or in circulatory insufficiency and hypoxia, sodium lactate may not be adequately metabolized; in these situations, sodium bicarbonate is the preferred agent. The usual initial dose is 1–2 mEq/kg. However, a more precise estimate of the dosage required is given by the general formula,

$$(C_d - C_a) \times k \times \text{body weight [in kg]} = \text{mEq required}$$

in which $C_d$ and $C_a$ represent, respectively, the serum bicarbonate concentration desired and the one measured, expressed in units of mEq/L; k represents that fraction of the total body weight in which the administered material is apparently (not actually) distributed. The k for bicarbonate or potential bicarbonate approximates 0.5–0.6. Such calculations indicate that 0.5 mL/kg of a molar solution of sodium bicarbonate would raise the serum bicarbonate concentration approximately 1 mEq/L. However, responses to administered bicarbonate vary widely because it may be sequestered in bone or muscle, lost in urine, or undergoing accelerated systemic consumption.

With renal insufficiency, acidosis should be corrected cautiously, because the sodium administered with bicarbonate may result in further expansion of the extracellular fluid volume and lead to hypertension or pulmonary edema. Patients are frequently asymptomatic and have "adjusted" to the acidemic state. Overcorrecting acidosis may lead to tetany if there is an associated hypocalcemia from vitamin D deficiency or phosphate retention. It is rarely necessary to increase serum bicarbonate levels acutely above 15 mEq/L unless the patient is symptomatic. If hyperphosphatemia coexists with acidosis, it should be treated simultaneously with low-phosphate diets and oral calcium carbonate.

Treating acidosis with sodium bicarbonate should always be considered a temporizing measure. Every attempt should be made to treat the underlying cause, such as using glucose and insulin in diabetic ketoacidosis; improving circulation in shock; eliminating salicylates, methanol, or other toxins; and treating underlying sepsis.

Severe metabolic acidosis is a part of cardiovascular shock of various causes (see Chapter 60). Because of differences in pH and $P_{CO_2}$ between arterial and central venous values in this situation, it is often useful to sample from arterial and central venous lines.

**ALKALOSIS.** Normally, the kidney has an enormous capacity to excrete bicarbonate, and increased amounts of blood bicarbonate are promptly excreted. However, under certain circumstances, *metabolic alkalosis* may develop and be maintained. Typically, it is caused by the administration of excess amounts of alkali, intravenously or orally as in milk alkali syndrome; by the loss of hydrogen ion through emesis from pyloric stenosis or nasogastric drainage; or by acute volume contraction with disproportionate losses of chloride. Severe hypokalemia can result in alkalosis or may perpetuate it (see Chapter 53).

When the plasma bicarbonate level is elevated, respiratory compensation may result in hypoventilation and an increase in $P_{CO_2}$. Rarely, respiration may be so depressed in infants with severe hypochloremic alkalosis that blood oxygenation is

diminished. Severe alkalotic tetany may also occur. In such instances, administering ammonium chloride may effect symptomatic improvement; the dose may be calculated from the general formula presented, with a probable k of 0.2–0.3. Such therapy only relieves symptoms and should not be used in place of correcting the contracted volume of body fluids or administering potassium chloride to repair intracellular deficits.

Metabolic alkalosis associated with volume contraction responds to measures designed to expand volume and replace the chloride and potassium deficits. It occurs in patients with acid-base disorders caused by vomiting, gastric suction, congenital chloride diarrhea, dietary chloride deficiency, or administration of diuretics. In this setting of chloride depletion, urinary chloride concentration is low (≤10 mM/L). A minority of patients are chloride resistant, with urinary chloride concentrations of 15 mM/L or greater because of hyperadrenalism, Bartter syndrome, severe potassium depletion, or licorice ingestion. Potassium repletion, using potassium chloride, not potassium phosphate, and specific therapy directed to the underlying condition are indicated.

*Respiratory alkalosis* occurs in salicylate intoxication; in various central nervous system diseases, such as severe hypoxic insult, trauma, infection, or tumors; with anxiety or fever; with overventilation on a respirator; and in congestive heart failure, hepatic insufficiency, and gram-negative septicemia. Treatment should be directed at removing the underlying cause, although measures designed to return the $Pco_2$ to normal may be indicated. Acidifying agents such as ammonium chloride are not indicated.

**HYPONATREMIA.** The serum sodium level is most commonly reduced as a result of true sodium depletion, water intoxication, or a combination of both (see Table 47–2). A low serum sodium level, thought to be a result of redistribution of total body sodium, may be associated with severe illnesses or occur in the terminally ill patient. *Apparent* hyponatremia, an artifact, may be seen in diabetic ketoacidosis when the water content of plasma is reduced by the presence of increased quantities of lipids. This error is avoided by laboratory methods that determine sodium activity rather than concentration.

Patients with a serum sodium level below 120 mEq/L are often symptomatic (e.g., convulsions, shock, lethargy), although this depends in part on the rate of change in serum sodium. Some patients with serum sodium values below 120 mEq/L, achieved over a period of several months, may be relatively asymptomatic.

The treatment of *asymptomatic hyponatremia* depends on its cause. With water overload, fluid restriction is the appropriate measure; the serum sodium level may return rapidly to normal if there is good renal function, but this may take several days or weeks for patients with SIADH. Adding extra salt to the diet or increasing the sodium concentration of parenterally administered fluid often corrects a sodium deficit.

Measuring urinary sodium concentration helps determine the cause of hyponatremia. Patients who have hyponatremia with a true deficit in total body sodium due to renal losses from diuretic excess, salt-losing nephritis, metabolic ketoacidosis, osmotic diuresis, or obstructive uropathy or to extrarenal losses from vomiting, diarrhea, third spacing, burns, or fistulas have clinical signs and symptoms of extracellular fluid volume depletion. Urinary sodium concentration is often greater than 20 mmol/L in renal salt-losing conditions and less than 10 mmol/L in other situations. Correction requires administration of isotonic saline. In patients in whom hyponatremia is caused by an excess of total body water (e.g., hypothyroidism, pain, use of certain drugs, SIADH), urinary sodium concentration usually exceeds 20 mmol/L, and therapy employs water restriction.

In patients who have excesses of sodium and water, edematous states such as nephrotic syndrome, cirrhosis, or cardiac failure, the urinary sodium level is usually less than 10 mmol/L; however, in edematous patients with acute and chronic renal failure, the urinary sodium level may be in excess of 20 mmol/L. Treatment for hyponatremia associated with edema due to excess water and salt retention is usually water intake and salt restriction. Inappropriate treatment may not correct an underlying defect and may be detrimental. In some patients, for example, although there is an excess of total body sodium and water, the effective plasma volume is reduced and may be further compromised by aggressive therapy directed toward correction of the edema. In other patients, administering sodium may result in further expansion of extracellular fluid volume without correcting the serum sodium level or, in the patient with renal insufficiency, may produce or exacerbate hypertension.

In the pediatric population, hyponatremia related to sodium deficiency most commonly occurs in conditions with excess gastrointestinal loss from emesis or diarrhea, excess renal loss through salt-losing nephritis and use of diuretics, or excess cutaneous salt losses with cystic fibrosis. Sodium deficiency may also occur in infants receiving inadequate parenteral sodium, such as very-low-birthweight infants who may have excessive urinary sodium losses. Perhaps the most common cause of hyponatremia due to insufficient dietary intake of sodium in an otherwise well population in the United States occurs with the *WIC syndrome*, named for the government aid program for poor women, infants, and children. These infants are fed diluted formula or water when eligible parents do not receive adequate infant formulas through the WIC food supplementation program. Providing adequate oral salt and water intake corrects this common problem, which should be readily identified by the physician through a careful history. Social service involvement is indicated. Water intoxication conditions not associated with true depletion of total body sodium are most commonly seen with SIADH occurring during central nervous system infections, asthma, the use of ventilatory machines, and in the postoperative period. Psychogenic polydipsia, reported even in toddlers, can mimic hyponatremia.

Treatment of *symptomatic hyponatremia* consists of administering a hypertonic saline solution, calculated according to the formula in the preceding section on acidosis, with k representing serum sodium rather than bicarbonate. Because there is osmotic equilibrium between cells and extracellular water, changes in osmolality are distributed over total body water so that the value for k should be 0.6–0.7 for the child and adolescent and 0.7–0.8 for the newborn or premature infant. A dose of 12 mL/kg of body weight of 3% sodium chloride solution (6 mEq sodium/kg) usually raises the serum sodium level by approximately 10 mEq/L. Rapid correction of hyponatremia may be associated with myelinolysis of the central nervous system in adults; there are few data regarding the occurrence and prevalence of this problem in children. The initial rapid therapeutic increase in the serum sodium level should only be to a value of about 125 mEq/L and only in the symptomatic individual. Subsequent elevation of serum sodium concentration should be effected in small increments over several hours. Hypernatremia should be avoided.

**HYPERNATREMIA.** Hypernatremia (see Table 47–1) may result from faulty preparation of infant formulas, as with the use of condensed instead of evaporated milk or heaped rather than level measures of milk powder. These errors increase the solute load excreted by the kidney relative to the amount of water provided and result in an osmotic diuresis and negative water balance.

*Salt poisoning* may occur through the accidental ingestion of excessive amounts of sodium chloride (e.g., table salt, sea water) by a child or the ingestion of accidental substitution of

reducing the likelihood of bacterial meningitis. The availability and application of each of these approaches is different for each of the three major causes of bacterial meningitis in children.

**Haemophilus influenzae Type b** (see Chapter 177). Rifampin prophylaxis should be given to all *household contacts*, including adults, if there are any close family members less than 4 yr old who have not been immunized fully. A household contact is one who lives in the residence of the index case or who has spent a minimum of 4 hr with the index case for at least 5 of 7 days preceding the patient's hospitalization. Family members should receive rifampin prophylaxis immediately after the diagnosis is confirmed in the index case because more than 50% of secondary family cases occur in the 1st week after the index patient has been hospitalized.

The risk of secondary cases of *H. influenzae* type b infection in *day-care center contacts* is less than that for household contacts and probably greater than that for the general population. The risk is exceedingly low for day-care center children who are nonclassroom contacts and those over 2 yr old. The efficacy of chemoprophylaxis in day-care centers is uncertain, and there are difficulties in ensuring that all at-risk day-care center attendees receive the drug. Chemoprophylaxis for children and adults in day-care centers that resemble households (e.g., >25 hr/wk of close contact) should be provided to all adults and children if two or more cases of *H. influenzae* type b infection occur within 60 days and some of the children are <2 yr of age and not fully immunized. The dose of rifampin is 20 mg/kg/24 hr (maximum 600 mg) given once each day for 4 days. Rifampin discolors the urine and sweat red-orange, stains contact lenses, and reduces the serum concentrations of some drugs, including oral contraceptives. Rifampin is contraindicated during pregnancy. In addition to prophylaxis, day-care center workers and parents should be educated about the signs of serious *H. influenzae* infection and the importance of seeking prompt medical attention for fever or other potential manifestations of *H. influenzae* disease.

The most exciting development in the prevention of childhood bacterial meningitis is the development and licensure of vaccines against *H. influenza* type b. The recently licensed conjugate vaccines have been shown to be safe and immunogenic in infants during the first months of life. Currently, four conjugate vaccines and a combination vaccine that combines one of these conjugates with diphtheria, pertussis, and tetanus toxoid (DPT) are licensed in the United States. Although each of these vaccines elicits different profiles of antibody response in infants immunized at 2–6 mo of age, all result in protective levels of antibody after two to four doses. Prelicensure studies demonstrated that each of the conjugate vaccines was effective, with efficacy rates ranging from 70% to 100%. Efficacy was not as consistent in Native American populations, a group recognized as having an extremely high incidence of disease. Postlicensure surveillance for cases of meningitis caused by *H. influenzae* type b also support a high degree of protection afforded by vaccination. As a result, the Committee on Infectious Diseases of the American Academy of Pediatrics recommends that all children should be immunized with an *H. influenzae* type b conjugate vaccine beginning at about 2 mo of age or as soon as possible thereafter.

*H. influenzae* type b nasopharyngeal colonization may not be eradicated despite 10 days of appropriate parenteral antibiotic therapy. Prior to discharge from the hospital, *the patient* should receive rifampin (20 mg/kg/dose every day for 4 days) to prevent introduction or reintroduction of the organism into the household or day-care center.

***Neisseria meningitidis.*** Chemoprophylaxis is recommended for all close contacts of patients with meningococcal meningitis regardless of age or immunization status. Close contacts should be treated wtih rifampin 10 mg/kg/dose every 12 hr for 2 days (maximum dose of 600 mg) as soon as possible after identification of a case of meningococcal meningitis or sepsis. Close contacts include household, day-care center, and nursery school contacts, and health care workers who have direct exposure to secretions (e.g., mouth-to-mouth resuscitation, suctioning, intubation). Exposed contacts should be treated immediately upon suspicion of infection in the index patient; bacteriologic confirmation of infection should not be awaited. In addition, all contacts should be educated about the early signs of meningococcal disease and the need to seek prompt medical attention if these signs develop.

Meninogococcal quadrivalent vaccine against serogropus A, C, Y, and W135 is recommended for high-risk children over 2 yr of age. High-risk patients include those with asplenia, functional splenic dysfunction, or deficiencies of terminal complement proteins. The vaccine may also be used as an adjunct with chemoprophylaxis for exposed contacts and during epidemics of meningococcal disease. Unfortunately, most cases of endemic meningococcal meningitis are due to group B, for which there currently is no effective vaccine.

***Streptococcus pneumoniae.*** No chemoprophylaxis or vaccination is required for normal hosts who may be contacts of patients with pneumococcal meningitis, as secondary cases rarely have occurred. High-risk patients should receive the 23-valent pneumococcal vaccine, and patients with sickle cell anemia should also receive chemoprophylaxis with daily oral penicillin, amoxicillin, or trimethoprim-sulfamethoxazole.

**PROGNOSIS.** Appropriate recognition, prompt antibiotic therapy, and supportive care have reduced the mortality of bacterial meningitis beyond the neonatal period to 1–8%. The highest mortality rates are observed with pneumococcal meningitis. Severe neurodevelopmental sequelae may occur in 10–20% of patients recovering from bacterial meningitis, and as many as 50% have some, albeit subtle, neurobehavioral morbidity. Prognosis is poorest among infants less than 6 mo and in those with more than $10^6$ CFU of bacteria/mL in their CSF. Those with seizures occurring more than 4 days into therapy, or with coma or focal neurologic signs on presentation, also tend to have more long-term sequelae. Interestingly, there is not a good correlation between duration of symtpoms prior to diagnosis of meningitis and outcome.

The most common neurologic sequelae include hearing loss, mental retardation, seizures, delay in acquisition of language, visual impairment, and behavioral problems.

Sensorineural hearing loss is the most common sequela of bacterial meningitis. It is due to labyrinthitis following cochlear infection and occurs in as many as 30% of patients with pneumococcal meningitis, 10% with meningococcal, and 5–20% of those with *H. influenzae* type b meningitis. Hearing loss may also be due to direct inflammation of the auditory nerve. Adjunctive therapy with dexamethasone may reduce the incidence of severe hearing loss. Regardless of the bacterial agent, type of antibiotic therapy, or use of dexamethasone, all patients with bacterial meningitis should undergo careful audiologic assessment before or soon after discharge from the hospital. Frequent reassessment on an outpatient basis is indicated for all patients who have a hearing deficit.

## 169.2 Viral Meningoencephalitis

Viral meningoencephalitis is an acute inflammatory process involving the meninges and, to a variable degree, brain tissue. These infections are relatively common and may be caused by a number of different agents. The CSF is characterized by pleocytosis and the absence of microorganisms on Gram stain and routine culture. In most instances the infections are self-

limited; in some cases, however, substantial morbidity and mortality may be observed.

**ETIOLOGY.** Although the specific etiologic agent is not identified in many instances, clinical and research experience indicate that viruses are usually the responsible pathogens, accounting for the seasonal pattern of disease. Enteroviruses cause more than 80% of all cases. Other frequent causes of infection include arboviruses and herpesviruses. Mumps is a common pathogen in regions where vaccine is not used widely.

**EPIDEMIOLOGY.** Because most cases are due to enteroviruses, the basic epidemiologic pattern of viral meningoencephalitis reflects their prevalence. Infection with enteroviruses is spread directly from person to person, and the incubation period is usually 4–6 days; most cases in temperate climates occur in the summer and fall. Epidemiologic considerations in aseptic meningitis due to agents other than enteroviruses also include season, geography, climatic conditions, animal exposures, and factors related to the specific pathogen.

**COMMON PATHOGENS.** Arboviruses are zoonoses in which humans, not being essential in the viral life cycle, are infected accidentally by an arthropod vector. Most commonly, mosquitoes or ticks acquire arboviruses by biting infected birds or small mammals, which often have prolonged viremia without illness. The insect vectors transmit the virus to other vertebrates, including humans and horses. Encephalitis in horses ("blind staggers") may be the first indication of an incipient epidemic. Although rural exposure is most common, urban and suburban outbreaks are also frequent. The most common arboviruses responsible for central nervous infection in the United States are St. Louis and California virus (see Chapter 225).

*Enteroviruses* are small RNA-containing viruses; 68 specific serotypes have been identified. The severity of disease ranges from mild, self-limited illness with primarily meningeal involvement to severe encephalitis with death or significant sequelae. Epidemics, some devastating, have been observed among newborns in nurseries.

*Herpes simplex virus type 1* (HSV-1) is an important cause of severe, sporadic encephalitis in children and adults. Infection may accompany primary or recurrent infection. Brain involvement usually is focal; progression to coma and death occurs in 70% of cases without antiviral therapy. Severe encephalitis with diffuse brain involvement is caused by *herpes simplex virus type 2* (HSV-2) in neonates who have contracted the virus from their mothers at delivery. A mild transient form of meningoencephalitis may accompany genital herpes infection in sexually active adolescents; most of these infections are caused by HSV-2. *Varicella-zoster virus* (VZV) may cause CNS infection in close temporal relationship with chickenpox. The most common manifestation of CNS involvement is cerebellar ataxia, and the most severe is an acute encephalitis. Following primary infection, VZV becomes latent in spinal and cranial nerve roots and ganglia, expressing itself later as herpes zoster, often with accompanying mild meningoencephalitis. *Cytomegalovirus* (CMV) infection of the CNS may be part of congenital infection or disseminated disease in compromised hosts, but it does not cause meningoencephalitis in normal infants and children. *Epstein-Barr virus* (EBV) has been associated with a myriad of CNS syndromes (see Chapter 215).

Meningoencephalitis is caused occasionally by respiratory viruses, rubeola, or rubella. Mumps meningoencephalitis is mild but deafness from damage to the 8th cranial nerve is not uncommon. Encephalitis caused by rabies is discussed in Chapter 227.

**PATHOGENESIS AND PATHOLOGY.** The sequence of events varies with the infecting agent and host. In general, viruses enter the lymphatic system, either through ingestion of enteroviruses; inoculation of mucous membranes by measles, rubella, VZV, or HSV; or by hematogenous spread from a mosquito or other insect bite. There, multiplication begins, and seeding of the bloodstream leads to infection of several organs. At this stage (the extraneural phase) a systemic, febrile illness is present, but if further viral multiplication takes place in the seeded organs, a secondary propagation of large amounts of virus may occur. Invasion of the CNS is followed by clinical evidence of neurologic disease. HSV-1 probably reaches the brain by direct spread along neuronal axons.

Neurologic damage is caused (1) by a direct invasion and destruction of neural tissues by actively multiplying viruses and/or (2) by a host reaction to viral antigens. Most neuronal destruction is probably due directly to viral invasion, whereas the host's vigorous tissue response induces demyelination and vascular and perivascular destruction.

Tissue sections of the brain generally are characterized by meningeal congestion and mononuclear infiltration, perivascular cuffs of lymphocytes and plasma cells, some perivascular tissue necrosis with myelin breakdown, neuronal disruption in various stages, including ultimately neuronophagia and endothelial proliferation or necrosis. A marked degree of demyelination with preservation of neurons and their axons is considered predominantly to represent "postinfectious" or "allergic" encephalitis. The cerebral cortex, especially the temporal lobe, is often severely affected by herpes simplex virus; the arboviruses tend to affect the entire brain; rabies has a predilection for the basal structures. Involvement of the spinal cord, nerve roots, and peripheral nerves is quite variable.

**CLINICAL MANIFESTATIONS.** The progression and ultimate severity of the clinical course is very much determined by the relative degree of meningeal and parenchymal involvement, which in turn is determined, at least in part, by the specific infectious agents. However, there is a wide range of severity of clinical manifestations, even with the same etiologic agent. Some children may appear to be mildly affected initially, only to lapse into coma and die suddenly. In others, the illness may be ushered in by high fever, violent convulsions interspersed with bizarre movements, and hallucinations alternating with brief periods of clarity, but then complete recovery.

The onset of illness is generally acute, although CNS signs and symptoms often are preceded by a nonspecific acute febrile illness of a few days' duration. The presenting manifestations in older children are headache and hyperesthesia, and in infants, irritability and lethargy. Headache is most often frontal or generalized; adolescents frequently note retrobulbar pain. Fever, nausea, and vomiting, pain in the neck, back, and legs, and photophobia are common. As the temperature rises, there may be mental dullness, eventuating in stupor in combination with bizarre movements, and convulsions. Focal neurologic signs may be stationary, progressive, or fluctuating. Loss of bowel and bladder control and unprovoked emotional bursts may occur.

Exanthems often precede or accompany the CNS signs, especially with echoviruses, coxsackieviruses, VZV, measles, and rubella. Examination often reveals nuchal rigidity without significant localizing neurologic changes, at least at the onset.

Specific forms or complicating manifestations of CNS viral infection include Guillain-Barré syndrome, acute transverse myelitis, acute hemiplegia, and acute cerebellar ataxia (see Chapter 547.1).

**LABORATORY ABNORMALITIES AND DIAGNOSIS.** The CSF contains from a few to several thousand cells per cubic millimeter. Early in the disease the cells are often polymorphonuclear; later mononuclear cells predominate. This change in cellular type is often demonstrated in CSF samples obtained 8–12 hr apart. The protein concentration in CSF tends to be normal or slightly elevated, but concentrations may be very high if brain destruction is extensive, as illustrated by HSV encephalitis in later stages. The glucose level is usually normal, although with

certain viruses, for example, mumps, a substantial depression of CSF glucose concentrations is often observed. The spinal fluid should be cultured for viruses, bacteria, fungi, and mycobacteria; in some instances special examinations are indicated for protozoa, mycoplasma, and other pathogens. The success of isolating viruses from the CSF of children with viral meningoencephalitis is determined by the time in the clinical course that the specimen is obtained, the specific etiologic agent, whether the infection is a meningitic as opposed to a localized encephalitic process, and the skill of the diagnostic laboratory. Isolating a virus is more likely early in the illness and the enteroviruses tend to be the easiest to isolate, although recovery of these agents from the CSF rarely exceeds 70%. In order to increase the likelihood of identifying the putative viral pathogen, specimens for culture also should be obtained from nasopharyngeal swabs, feces, and urine. Although isolating a virus from one or more of these sites does not prove causality, it is highly suggestive.

A serum specimen should be obtained early in the course of illness and, if viral cultures are not diagnostic, again 2–3 wk later for serologic studies. Serologic methods are not practical for diagnosing CNS infections caused by the enteroviruses because there are too many potential serotypes. This approach may be useful to confirm that a case is caused by a known circulating viral type. Serologic tests also may be of value in determining the etiology of nonenteroviral CNS infection. Newer diagnostic techniques for suspected viral meningoencephalitis that use polymerase chain reaction to detect viral DNA or RNA in CSF appear to be promising but are not yet clinically available.

Other tests of potential value in the evaluation of patients with suspected viral meningoencephalitis include an electroencephalogram and neuroimaging studies.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS.** A number of clinical conditions that cause CNS inflammation mimic viral meningoencephalitis. The most important group of alternate infectious agents to consider is bacteria. Most children with bacterial infections of the CNS have a more acute onset and appear more critically ill, but this is not always the case. Meningitis caused by the most common bacteria invading the CNS, *H. influenza* type B, *S. pneumoniae*, and *N. meningitidis*, may be insidious in onset. CNS infection caused by other bacteria, such as tuberculosis, *T. pallidum* (syphilis), *Borralia burgdorferi* (Lyme disease), and the bacillus associated with cat-scratch disease, also may have very indolent courses. Analysis of CSF and appropriate serologic tests is necessary to differentiate these bacterial and viral pathogens. Parameningeal bacterial infections, such as brain abscess or subdural or epidural empyema, may have features similar to viral CNS infections. CNS imaging procedures are critical for the diagnosis of these processes.

Nonbacterial infectious agents also need to be considered in the differential diagnosis of CNS infections. These agents include *Rickettsia, Mycoplasma, Protozoa,* and other parasites, and a number of fungi. Consideration of these agents usually arises as a result of accompanying symptoms, geographic distribution of infection, and/or host immune factors.

A variety of noninfectious disorders also may be associated with CNS inflammation and have manifestations overlapping with those associated with viral meningoencephalitis. Some of these disorders include: malignancy, collagen-vascular diseases, intracranial hemorrhage, and exposure to certain drugs or toxins. Attention to history and other organ involvement usually allows early elimination of these diagnostic possibilities. Recent exposure to possibly infected persons, animals, mosquitos and ticks, and any recent travel should be noted. Inquiry should also be made about recent injections of biologic substances and about the possibilities of exposure to heavy metals, pesticides, or noxious substances.

**PREVENTION.** The widespread use of effective attenuated viral vaccines for polio, measles, mumps, and rubella has almost eliminated CNS complications from these diseases in the United States. The availability of domestic animal vaccine programs against rabies has reduced the frequency of rabies encephalitis. The control of encephalitis due to arboviruses has been less successful because specific vaccines for the arboviral diseases that occur in North America are not available. However, control of insect vectors by suitable spraying methods and eradication of insect breeding sites reduce the incidence of these infections.

**TREATMENT.** Until a bacterial cause is excluded, parenteral antibiotic therapy should be administered. With the exception of the use of acyclovir for herpes simplex encephalitis, treatment of viral meningoencephalitis is nonspecific. For mild infections, treatment is limited to providing symptomatic relief, whereas for severe infection it is aimed at maintaining life and supporting each organ system.

Headache and hyperesthesia are treated with rest, non-aspirin-containing analgesics, and a reduction in room light, noise, and visitors. Acetaminophen is recommended for fever. Codeine, morphine, and the phenothiazine derivatives may be necessary for pain and vomiting, but, if possible, their use in children should be minimized because they may induce misleading signs and symptoms.

It is crucial to anticipate and be prepared for convulsions, cerebral edema, hyperpyrexia, inadequate respiratory exchange, disturbed fluid and electrolyte balance, aspiration and asphyxia, and cardiac or respiratory arrest of central origin.

Therefore, all patients with severe encephalitis should be monitored carefully. In patients with evidence of increased intracranial pressure, placement of a pressure transducer in the epidural space may be indicated for monitoring intracranial pressure as a guide to therapy aimed at reducing cerebral edema. The risks of cardiac and respiratory failure or arrest are high. All fluids, electrolytes, and medications are initially given parenterally. In prolonged states of coma, parenteral alimentation is indicated. Inappropriate secretion of antidiuretic hormone is quite common in acute CNS disorders, so that constant evaluation is required for its early detection. Normal blood levels of glucose, magnesium, and calcium must be maintained in order to minimize the threat of convulsions. If cerebral edema or seizures become evident, vigorous treatment should be instituted.

Supportive and rehabilitative efforts are very important after the patient recovers. Motor incoordination, convulsive disorders, squint, total or partial deafness, and behavioral disturbances may appear only after an interval of time. Visual disturbances due to chorioretinopathy and perceptual amblyopia may also have a delayed appearance. Special facilities and, at times, institutional placement may become necessary. Some sequelae of infection may be very subtle. Therefore, neurodevelopmental and audiologic evaluations should be part of the routine follow-up of children who have recovered from viral meningoencephalitis, even if they appear to be grossly normal.

**PROGNOSIS.** Most children completely recover from viral infections of the CNS, although prognosis depends upon the severity of the clinical illness, the specific etiology, and the age of the child. If the clinical illness is severe with evidence of substantial parenchymal involvement, the prognosis is poor, with potential deficits being intellectual, motor, psychiatric, epileptic, visual, or auditory in nature. Severe sequelae also should be anticipated in those with infection caused by HSV. Although some literature suggests that infants who contract viral meningoencephalitis have a poorer long-term outcome than older children, recent data refute this observation. Although about 10% of children younger than 2 yr of age with enteroviral CNS infections manifest an acute complication such as seizures, increased intracranial pressure, or coma, almost all have favorable long-term neurologic outcomes.

vidualized, and it is important that the dosage schedule be adjusted to allow patients to revert to mild polyuria before the next dose is given. For patients requiring over 10 μg/dose, a nasal spray preparation is also available. A parenteral preparation of DDAVP (0.03–0.15 μg/kg) is available and is useful postoperatively, particularly after transsphenoidal surgery, when nasal packing precludes nasal insufflation.

Great care must be taken in patients with DI who are comatose, undergoing surgery, or receiving intravenous fluids for any reason. Regardless of the form of therapy, any effective dose should be repeated only after its effect has worn off and polyuria recurs. Postoperative DI is often transient; daily reassessment of the need for antidiuretic hormone is necessary after it has been initiated.

DDAVP also has an effect on $V_2$-like extrarenal receptors, resulting in release of factor VIII and von Willebrand factor. Selected patients with mild or moderate hemophilia A or von Willebrand disease can be successfully treated with doses of DDAVP 15 times higher than the dose used for antidiuresis. Desmopressin is being increasingly used in the management of children with enuresis. Some of these children have been said to have nocturnal deficiency of vasopressin secretion, but this is not established. The dose required is slightly higher (20–40 μg) than that used to treat neurogenic DI. It is given as a nasal spray before bedtime.

### 513.1 Nephrogenic Diabetes Insipidus

(Vasopressin Receptor Defects)

See Chapter 484.

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## CHAPTER 514

# Inappropriate Secretion of Antidiuretic Hormone

(Hypersecretion of Vasopressin)

*Angelo M. DiGeorge*

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is now recognized as one of the most common aberrations of arginine vasopressin (AVP) secretion. In this condition, plasma levels of AVP are inappropriately high for the concurrent osmolality of the blood and are not suppressed by further dilution of body fluids.

**ETIOLOGY.** The syndrome is recognized in an increasing number of clinical conditions, particularly those involving the central nervous system, including meningitis, encephalitis, brain tumor and abscesses, subarachnoid hemorrhage, Guillain-Barré syndrome, head trauma, and after transsphenoidal surgery for pituitary tumors. Pneumonia, tuberculosis, acute intermittent porphyria, cystic fibrosis, infant botulism, perinatal asphyxia, use of positive-pressure respirators, and certain drugs such as vincristine and vinblastine also produce the syndrome. The mechanism of the disturbed regulation of AVP in these conditions is not fully understood, but in many instances, there is direct involvement of the hypothalamus. The syndrome has been observed in patients with Ewing sarcoma; with malignant tumors of the pancreas, duodenum, or thymus; and particularly with oat cell carcinoma of the lung. In these instances, the tumor presumably synthesizes and secretes AVP, with the syndrome disappearing when the tumor is removed. In rare cases, no cause for the syndrome has been found.

The syndrome has occurred during chlorpropamide therapy for diabetes mellitus, presumably because this drug potentiates AVP. Patients with diabetes insipidus treated with various antidiuretic preparations readily develop the syndrome during periods of excessive ingestion of fluids or during intravenous fluid therapy.

**CLINICAL MANIFESTATIONS.** The syndrome is probably most often latent and asymptomatic and forms the basis for the observation that serum sodium levels may be unexpectedly low in conditions such as pneumonia, tuberculosis, and meningitis. Careful attention to fluid replacement in patients with conditions known to be associated with the syndrome may prevent the development of symptoms.

The clinical manifestations are attributable to hypotonicity of body fluids and are those of water intoxication. If the serum sodium level is not below 120 mEq/L, there may be no symptoms. Early, the loss of appetite is followed by nausea and sometimes by vomiting. Irritability and personality changes, including hostility and confusion, may occur. When the serum sodium level falls below 110 mEq/L, neurologic abnormalities or stupor is common, and convulsive seizures may occur. Skin turgor and blood pressure are normal, and there is no evidence of dehydration.

**LABORATORY DATA.** Serum sodium and chloride concentrations are low, but the serum bicarbonate level usually remains normal. Despite low serum sodium, there is continued renal excretion of sodium. The serum is hypo-osmolar, but the urine is less than maximally dilute, and its osmolality is greater than

appropriate for the tonicity of the serum. Hypouricemia is common, probably because of increased urate clearance secondary to volume expansion. Concurrence of hypouricemia with hyponatremia is a clue to the diagnosis of SIADH and is especially helpful in the neonate. Renal and adrenal functions are normal.

**TREATMENT.** Successful treatment of the underlying disorder (e.g., meningitis, pneumonia) is followed by spontaneous remission. Immediate management of the hyponatremia consists simply of *restriction of fluids*. Sodium should be made available to replace the sodium loss; hypertonic saline solution is usually of little benefit, because even large sodium loads are excreted in the urine. In cases of severe water intoxication, with convulsions or coma, administration of hypertonic saline solution increases osmolality and controls the central nervous system manifestations. In such emergencies, administration of furosemide with 300 mL/m² of 1.5% sodium chloride causes a rise in sodium levels and diuresis. Demeclocycline interferes with the action of AVP on the renal tubule. Experience in adults with SIADH indicates that this agent may be useful, but its role in the treatment of children is not established. An 8-yr-old child with chronic SIADH has been successfully treated with single daily doses of furosemide.

## 514.1 Cerebral Salt Wasting

Children with acute or chronic central nervous system damage may develop a distinctive syndrome of salt wasting. The disorder has been associated with head trauma, central nervous system surgery, tumor, or meningitis. These children, unlike those with SIADH, have hypovolemia, excessive urine flow rate while receiving maintenance fluids, a large net loss of sodium, and a decreased plasma concentration of ADH. Levels of natriuretic hormone (ANH) are increased, but plasma renin and aldosterone levels are decreased; this suggests the syndrome is caused by inappropriate secretion of ANH. Therapy consists of volume-for-volume replacement of the urine loss with a 0.9% or 3% solution of sodium chloride. The condition usually remits but may recur and, in some instances, persists.

# Chapter 515

# Hyperpituitarism

*Angelo M. DiGeorge*

Hypersecretion of pituitary hormones is an expected finding in conditions in which deficiency of a target organ gives decreased hormonal feedback, as in primary hypogonadism or hypoadrenalism. In primary hypothyroidism, pituitary hyperfunction and hyperplasia can enlarge and erode the sella and, on rare occasions, increase intracranial pressure. Such changes should not be confused with primary pituitary tumors; they disappear when the underlying thyroid condition is treated. Pituitary hyperplasia also occurs in response to stimulation by ectopic production of releasing hormones such as that seen occasionally in patients with Cushing syndrome, secondary to corticotropin-releasing hormone excess, or in children with acromegaly secondary to growth hormone–releasing hormone (GHRH) produced by a variety of systemic tumors.

Primary hypersecretion of pituitary hormones by a suspected or proved adenoma is rare in childhood. The most commonly encountered pituitary tumors are those that secrete corticotropin, prolactin, or growth hormone (GH). With rare exceptions, pituitary adenomas that secrete gonadotropins or thyrotropin occur in adults. Hypothalamic hamartomas that secrete gonadotropin-releasing hormone are known to cause precocious puberty. It is suspected that some pituitary tumors may result from stimulation with hypothalamic-releasing hormones and in other instances, as in McCune-Albright syndrome, the tumor is caused by constitutive activating mutation of the $G_s\alpha$ gene. Any pituitary tumor may also cause various hormonal deficiencies by compressing pituitary tissue.

### PITUITARY GIGANTISM AND ACROMEGALY

In young persons with open epiphyses, overproduction of GH results in gigantism; in persons with closed epiphyses, the result is acromegaly. Often, some acromegalic features are seen with gigantism, even in children and adolescents; after closure of the epiphyses, the acromegalic features become more prominent.

**ETIOLOGY.** Pituitary gigantism is rare. The cause is most often a pituitary adenoma, but gigantism has been observed in a 2.5-yr-old boy with a hypothalamic tumor that presumably secreted GHRH. Other tumors, particularly in the pancreas, have produced acromegaly by secretion of large amounts of GHRH with resultant hyperplasia of the somatotrophs; GHRH was first isolated from two such pancreatic tumors. The GH-secreting adenomas associated with McCune-Albright syndrome are caused by an activating mutation of the $G_s\alpha$ gene (see Chapter 517).

**CLINICAL MANIFESTATIONS.** The usual manifestations consist of rapid linear growth, coarse facial features, and enlarging hands and feet. In young children, rapid growth of the head may precede linear growth. Some patients have behavioral and visual problems. In most of the recorded cases, the abnormal growth became evident at puberty, but the condition has been established as early as the newborn period in one child and at 21 mo of age in another. Giants may grow to a height of 8 ft or more. Acromegaly consists chiefly of enlargement of the distal parts of the body, but manifestations of abnormal growth involve all portions. The circumference of the skull increases, the nose becomes broad, and the tongue is often enlarged, with coarsening of the facial features. The mandible grows excessively, and the teeth become separated. The fingers and toes grow chiefly in thickness. There may be dorsal kyphosis. Fatigue and lassitude are early symptoms. Delayed sexual maturation or hypogonadism may occur. Signs of increased intracranial pressure appear later; visual loss may be demonstrable only on careful examination of visual fields.

**LABORATORY DATA.** GH levels are elevated and may occasionally reach 400 ng/mL. The episodic pattern of secretion and the nocturnal surge may be preserved in some patients. There is usually no suppression of GH levels by the hyperglycemia of a glucose tolerance test. There may be no response, normal responses, or paradoxical responses to various other stimuli. For example, L-dopa may paradoxically decrease GH levels. Administration of thyrotropin-releasing hormone results in increased GH levels in some acromegalics, and in a 5-yr-old giant, it resulted in a threefold increase in levels of GH. Insulin-like growth factor-I (IGF-I) levels are consistently elevated in acromegaly, in one study ranging from 2.6–21.7 U/mL; normal levels are 0.3–1.4 U/mL. Most patients also have marked hyperprolactinemia as a result of plurihormonal adenomas that secrete GH and prolactin.

Adenomas may compromise other anterior pituitary func-

idly leading to coma; ketotic hyperglycinemia in which seizures are associated with vomiting, fluid and electrolyte disturbances, and a metabolic acidosis; and Leigh disease suggested by elevated levels of serum and CSF lactate or an increased lactate/pyruvate ratio. A comprehensive description of the diagnosis and management of these metabolic diseases is discussed in Part X.

The unintentional *injection of a local anesthetic* into the fetus during labor can produce intense tonic seizures. These infants are often thought to have had a traumatic delivery because they are flaccid at birth, they have abnormal brain stem reflexes, and they show signs of respiratory depression that sometimes requires ventilation. Examination may show a needle puncture of the skin or a perforation or laceration of the scalp. An elevated serum anesthetic level confirms the diagnosis. The treatment consists of supportive measures and promotion of urine output by IV fluids with appropriate monitoring to prevent fluid overload.

*Pyridoxine dependency,* a rare disorder, must be considered when generalized clonic seizures begin shortly after birth with signs of fetal distress in utero. These seizures are particularly resistant to conventional anticonvulsants, such as phenobarbital or phenytoin. The history may suggest that similar seizures occurred in utero. Some cases of pyridoxine dependency are reported to begin later in infancy or in early childhood. This condition is inherited as an autosomal recessive. Although the precise biochemical defect is unknown, pyridoxine is essential for the synthesis of glutamic acid decarboxylase, which in turn is required for the synthesis of GABA. In these infants, large amounts of pyridoxine are required to maintain adequate production of GABA. When pyridoxine-dependent seizures are suspected, 100- to 200-mg of pyridoxine should be administered IV during the EEG, which should be promptly provided once the diagnosis is considered. The seizures will abruptly cease, and the EEG will normalize during the next few hours. In the future, measurement of CSF and plasma pyridoxal-5-phosphate may prove to be the more precise method of confirming the diagnosis of pyridoxine dependency. These children require lifelong supplementation of oral pyridoxine, 10 mg/day. Generally, the earlier the diagnosis and therapy with pyridoxine, the more favorable will be the outcome. Untreated children have persistent seizures and are uniformly severely mentally retarded (see also Chapter 43.7).

*Drug withdrawal seizures* can present in the newborn nursery but may take several weeks to develop because of prolonged excretion of the drug by the neonate. The incriminated drugs include barbiturates, benzodiazepines, heroin, and methadone. The infant may be jittery, irritable, and lethargic and may show myoclonus or frank clonic seizures. The mother may deny the use of drugs; a serum or urine analysis may identify the responsible agent (see Chapter 92).

Infants with severe *cytoarchitectural abnormalities* of the brain including lissencephaly, schizencephaly, neonatal adrenoleukodystrophy, and chromosome abnormalities are susceptible to severe seizures. The investigation of these infants may include a karyotype, CT scanning, MRI, and a long-chain fatty acid determination.

**TREATMENT.** Anticonvulsants should be utilized in the management of infants with seizures secondary to hypoxic-ischemic encephalopathy or an acute intracranial bleed (Chapters 84.7 and 85). The dose and administration of phenobarbital, diazepam, and other medications for the treatment of neonatal seizures are discussed in Chapter 84.7. The greater use of EEG recording in the infant with subtle seizures has identified a number of patients with abnormal movements unrelated to seizure discharges; anticonvulsants are not indicated for this group of neonates.

**PROGNOSIS.** This depends mainly on the primary cause of the disorder or the severity of the insult. In the case of the hypoglycemic infant of the diabetic mother or hypocalcemia associated with excessive phosphate feedings, the prognosis is excellent. Conversely, the child with intractable seizures due to severe hypoxic-ischemic encephalopathy or a cytoarchitectural abnormality of the brain will usually not respond to anticonvulsants and is susceptible to status epilepticus and early death. The challenge for the physician is to identify patients who will recover with prompt treatment and to avoid delays in diagnosis that could lead to severe irreversible neurologic damage.

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## 543.6 Status Epilepticus

Status epilepticus is defined as a continuous convulsion lasting greater than 30 min or the occurrence of serial convulsions between which there is no return of consciousness. Status epilepticus may be classified as generalized (tonic-clonic, absence) or partial (simple, complex, or with secondary generalization). Generalized tonic-clonic seizures predominate in cases of status epilepticus. Status epilepticus is a medical emergency that requires an organized and skillful approach in order to minimize the associated mortality and morbidity.

**ETIOLOGY.** There are three major subtypes of status epilepticus in children: prolonged *febrile seizures, idiopathic status epilepticus* in which a seizure develops in the absence of an underlying CNS lesion or insult, and *symptomatic status epilepticus* when the seizure occurs in association with a longstanding neurologic disorder or a metabolic abnormality. A febrile seizure lasting for more than 30 min, particularly in a child less than 3 yr of age, is the most common cause of status epilepticus. The idiopathic group includes epileptic patients who have had sudden withdrawal of anticonvulsants (especially benzodiazepines and barbiturates) followed by status epilepticus. Epileptic children who are given anticonvulsants on an irregular basis or who are noncompliant are more likely to develop status epilepticus. Status epilepticus may also be the initial presentation of epilepsy. Sleep deprivation and an intercurrent infection tend to render epileptic patients more susceptible to status epilepticus. The mortality and morbidity among patients with prolonged febrile seizures and idiopathic status epilepticus are low. Status epilepticus owing to other causes has a much higher mortality and the cause of death is usually directly attributable to the underlying abnormality. Unlike those with idiopathic status epilepticus, many of these children have not previously had a

convulsion. Severe anoxic encephalopathy presents with seizures during the first few days of life, and the ultimate prognosis relates partly to the ease in controlling the seizures. A prolonged convulsion may be the initial manifestation of encephalitis, and epilepsy may be a long-term complication of meningitis. Infants with congenital malformations of the brain (e.g., lissencephaly or schizencephaly) may have recurrent episodes of status epilepticus that are frequently refractory to anticonvulsants. Metabolic inborn errors of metabolism may present with status epilepticus in the newborn. These infants often have a progressive loss of consciousness associated with failure to thrive and excessive vomiting. Electrolyte abnormalities, hypocalcemia, hypoglycemia, drug intoxication, Reye syndrome, lead intoxication, extreme hyperpyrexia, and brain tumors, particularly in the frontal lobe, are additional causes of status epilepticus.

**PATHOPHYSIOLOGY.** The relationship between the neurologic outcome and the duration of status epilepticus is unknown in children and adults. There is some evidence that the period of status epilepticus that produces neuronal injury in a child is less than that for an adult. In the primate, pathologic changes can occur in the brain of the ventilated animal after 60 min of constant seizure activity when metabolic homeostasis is maintained. Thus, cell death may result from excessively increased metabolic demands by continually discharging neurons. The most vulnerable areas of the brain include the hippocampus, amygdala, cerebellum, middle cortical areas, and the thalamus. Characteristic acute pathologic changes consist of venous congestion, small petechial hemorrhages, and edema. Ischemic cellular changes are the earliest histologic finding, followed by neuronophagia, microglial proliferation, cell loss, and increased numbers of reactive astrocytes. Prolonged seizures are associated with lactic acidosis, an alteration in the blood-brain barrier, and elevation of intracranial pressure. A series of complex, poorly understood hormonal and biochemical changes ensues. Circulating levels of prolactin, adrenocorticotropic hormone, cortisol, glucagon, growth hormone, insulin, epinephrine, and cyclic nucleotides are elevated during status epilepticus in the animal. Neuronal concentrations of calcium, arachidonic acid, and prostaglandins rise and may promote cell death. Initially, the animal may be hyperglycemic, but ultimately hypoglycemia occurs. Inevitably, dysfunction of the autonomic nervous system develops, which may lead to hypotension and shock. Constant tonic-clonic muscle activity during a seizure may produce myoglobinuria and acute tubular necrosis.

Several investigations have shown significant increases in cerebral blood flow and metabolic rate during status epilepticus. In the animal, approximately 20 min of status epilepticus produces regional oxygen insufficiency, which promotes cell damage and necrosis. These studies have led to the concept of a critical period during status epilepticus when irreversible neuronal changes may develop. This *transitional period* varies between 20 and 60 min in the animal during constant seizure activity. Management of the child should be directed to supporting vital functions and to controlling the convulsions as expeditiously as possible, because the precise transitional period in humans is unknown.

**TREATMENT.** The *initial management* of the patient begins with an assessment of the respiratory and cardiovascular systems. The child should be transferred to an intensive care unit if possible. The oral airway is inspected for patency, and the pulse, temperature, respirations, and blood pressure are recorded. Excessive oral secretions are removed by gentle suction, and a properly fitting face mask attached to oxygen is applied. If the patient does not respond to oxygen by mask or is difficult to ventilate by an Ambu Bag, consideration should be given to intubation and assisted ventilation. An IV catheter is immediately inserted. If hypoglycemia is confirmed by Dextrostix, a rapid infusion of 5 mL/kg of 10% dextrose is provided. Blood is obtained for a CBC, electrolytes (including calcium and magnesium), glucose, creatinine, and anticonvulsant levels, if indicated. Blood and urine may be obtained for toxicology, keeping in mind that some drugs potentiate or precipitate status epilepticus (e.g., amphetamines, cocaine, phenothiazines, theophylline in toxic levels, and the tricyclic antidepressants). Arterial blood gases should be determined, and it is wise to maintain an arterial line for repeated examinations. Examination of the CSF is imperative if meningitis or encephalitis is considered, unless there is a contraindication for the procedure. In this case, appropriate antibiotics should be administered, followed by imaging studies, before the lumbar puncture is attempted. If the seizures are refractory to anticonvulsants, or the patient is paralyzed and is on a respirator, continuous EEG monitoring is important to follow the frequency of seizure discharges, their location, and the response to anticonvulsant therapy.

A physical and neurologic examination should be carried out concurrently to assess evidence of trauma; papilledema, a bulging anterior fontanel, or lateralizing neurologic signs suggesting increased intracranial pressure; manifestations of sepsis or meningitis; retinal hemorrhages that may indicate a subdural hematoma; Kussmaul breathing and dehydration suggestive of metabolic acidosis or irregular respirations signifying brain stem dysfunction; evidence of failure to thrive, a peculiar body odor, or abnormal hair pigmentation that suggests an inborn error of metabolism; and constriction or dilatation of pupils suggesting a toxin or drugs as the cause of the status epilepticus. A comprehensive examination should be undertaken once the seizures are under control. Further investigation of the patient including neuroradiologic studies depends on the physical and neurologic findings and on a precise history of the seizure type and frequency.

*Drugs* should always be delivered IV in the management of status epilepticus; the IM route is unreliable because some drugs are bound by muscle. One of the major problems in the management of status epilepticus is the inappropriate use of anticonvulsants. Too often an unsuitably low drug dose is given, and with lack of response, another antiepileptic is introduced immediately. Care should be given with regard to how the anticonvulsant is delivered. Phenytoin forms a precipitate in glucose solutions and is rendered ineffective. Other drugs interact with plastic containers or are altered by sunlight (e.g., paraldehyde). It is essential to have resuscitation equipment at the bedside and the ability to intubate and ventilate the patient immediately if respiratory depression should supervene.

Either *diazepam* or *lorazepam* may be used initially, because they are effective for the immediate control of prolonged tonic-clonic seizures in most children. Diazepam should be given IV directly into the vein (not the tubing) with a dose of 0.3 mg/kg and with a maximum dose of 10 mg at a rate no greater than 1 mg/min. Respiratory depression and hypotension can occur, especially if administered with a barbiturate. Diazepam is effective in the management of tonic-clonic status, but the drug has a short half-life so that the seizures will recur unless a longer acting anticonvulsant is administered simultaneously. Lorazepam is an equally effective short-term anticonvulsant, with a greater duration of action and decreased likelihood of producing hypotension and respiratory arrest. The recommended dose is 0.05–0.1 mg/kg administered slowly, IV. If an IV line cannot be established or the child is some distance from a medical center, rectal diazepam or lorazepam can be used safely. Undiluted diazepam is placed into the rectum by a syringe and a flexible tube at a dose of 0.3–0.5 mg/kg. The effective dose of rectal lorazepam is 0.05–0.1 mg/kg. Therapeutic serum levels occur within 5–10 min. Sublingual lorazepam may be used to treat children with serial seizures that tend to develop into status epilepticus while the children are at home.

The dose of sublingual lorazepam is 0.05–0.1 mg/kg. The tablet is placed under the patient's tongue and dissolves in a few seconds.

Following the administration of diazepam or lorazepam, several options are available for further management. If the convulsive activity ceases after diazepam or lorazepam therapy or if the seizures persist, *phenytoin* is given immediately. The loading dose of phenytoin is 15–20 mg/kg IV at the rate of 1 mg/kg/min. Phenytoin may be safely added to half-normal or normal saline but not to glucose solutions; the undiluted drug can cause pain, irritation, and phlebitis of the vein. An electrocardiogram tracing is recommended during the loading phase in order to identify arrhythmias, a rare complication in children. If the seizures do not recur, a maintenance dose of 5–8 mg/kg divided into two equal doses daily is begun 12–24 hr later. Serum phenytoin levels should be monitored as the maintenance dose varies considerably with age. Phenytoin is not always effective in controlling tonic-clonic status epilepticus, in which case an alternative drug is necessary. In some centers, *phenobarbital* is initiated before phenytoin. It is given in a loading dose of 10–15 mg/kg or in the neonate 20 mg/kg IV during 10–30 min. With control of the seizures, the maintenance dose is 3–5 mg/kg/24 hr divided into two equal doses.

If the status epilepticus is not controlled by the preceding strategy, the physician must make some important therapeutic decisions, because it is likely the *transitional period* has passed. The choices for further drug management include paraldehyde, a diazepam drip, lidocaine, pentobarbital coma, or general anesthesia. By this stage the patient is usually sedated and may show signs of respiratory depression, necessitating elective intubation and assisted ventilation.

*Paraldehyde* is an excellent anticonvulsant and is relatively safe for administration to children. A 5% solution of paraldehyde is prepared by adding 1.75 mL of paraldehyde (1 g/mL) to $D_5W$ to a total volume of 35 mL. The loading dose is 150–200 mg/kg IV slowly for 15–20 min, and then seizure control is maintained with an infusion of 20 mg/kg/hr in a 5% concentration in a glass bottle, because the drug is incompatible with plastic. The IV drip rate may be lowered as the seizures and EEG improve. The drug should be freshly opened, because outdated paraldehyde can deteriorate to acetylaldehyde and acetic acid. Paraldehyde administered rectally or IM can produce tissue damage and sloughing, thus these routes should be reserved for exceptional circumstances.

A **diazepam constant infusion** may be considered rather than paraldehyde, particularly if the initial loading dose of diazepam briefly controlled the seizures. Diazepam is soluble in sterile water, normal saline, and Ringer lactate. A dilution of 0.04 mg/mL offers the greatest assurance of redissolution of diazepam and 24-hr stability. The suggested flow rate is 2–3 mg/hr, but the dose should be titrated against the patient's response and side effects.

If the status epilepticus persists following diazepam or lorazepam, and a trial of phenytoin, phenobarbital, and paraldehyde, serious consideration should be given to the induction of **pentobarbital coma.** In an intensive care setting, the patient is placed on a ventilator and a continuous EEG monitor. The initial IV loading dose of pentobarbital is 3–5 mg/kg followed by 2–3 mg/kg/hr to maintain the serum pentobarbital level between 25 and 40 μg/mL. A burst-suppression EEG pattern is maintained for a minimum of 48 hr, followed by cessation of the pentobarbital until the serum level falls to the therapeutic range. Pentobarbital coma requires careful monitoring by an experienced physician, because hypotension requiring pressor agents and electrolyte abnormalities are likely to occur.

**General anesthesia** is an alternative adjunct to the management of status epilepticus if conventional drug therapy is not effective or if pentobarbital coma is not an option. Several agents have been used successfully, including halothane and isoflurane. General anesthesia probably acts by reversing cerebral anoxia and the concomitant metabolic abnormalities, allowing the previously administered anticonvulsants to exert their effect. The major disadvantage of general anesthesia is that it must be administered in an operating room with anesthetic gas scavenging equipment for prolonged periods.

**Sodium valproate** has been an effective anticonvulsant in the management of several types of seizures. Because sodium valproate is not available parenterally, it must be given orally or rectally in patients with status epilepticus. Because vomiting and paralytic ileus are common in children with recurrent seizures, sodium valproate should be administered rectally during status epilepticus in order to achieve maximal absorption. Sodium valproate syrup (50 mg/mL) is diluted 1:1 with tap water and is given as a retention enema in a loading dose of 20 mg/kg. It may be considered in the management of status epilepticus in patients who do not respond to the conventional anticonvulsants and pentobarbital coma.

The use of anticonvulsant therapy following status epilepticus is controversial. There is little question that a long-term antiepileptic should be maintained in the child with a progressive neurologic disorder or with a history of recurrent seizures before the onset of status epilepticus. However, it is unlikely that a lengthy period of anticonvulsant treatment is necessary following an initial attack of idiopathic status epilepticus, particularly when a prolonged febrile seizure was the cause. Anticonvulsant therapy is maintained arbitrarily for 3 mo in this case and is discontinued if the child remains asymptomatic.

**PROGNOSIS.** The neurologic outcome following status epilepticus has improved significantly since the advent of modern pediatric intensive care units and the aggressive management of prolonged seizures. The mortality rate of status epilepticus is approximately 5% in most series. Most deaths occur in the symptomatic group, most of whom have a serious and life-threatening CNS disorder known before the onset of status epilepticus. In the absence of a progressive neurologic insult or metabolic disorder, the morbidity from status epilepticus is low. The fact that long-term sequelae such as hemiplegia, extrapyramidal syndromes, mental retardation, and epilepsy are more common in children less than 1 yr of age following status epilepticus is related to the fact that this group is more likely to have a premorbid underlying CNS disorder than the older child.


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# Chapter 548
# Encephalopathies

*Encephalopathy* is a term used to describe a generalized disorder of cerebral function that may be acute or chronic, progressive or static. The etiology of the encephalopathies in children includes infectious, toxic (e.g., carbon monoxide, drugs, lead), metabolic, and ischemic causes. Hypoxic-ischemic encephalopathy is discussed in Chapter 84.

## 548.1 Cerebral Palsy

See also Chapters 40 and 41.

Cerebral palsy (CP) is a static encephalopathy that may be defined as a nonprogressive disorder of posture and movement, often associated with epilepsy and abnormalities of speech, vision, and intellect resulting from a defect or lesion of the developing brain. CP is a common disorder, with an estimated prevalence of 2/1,000 population. The condition was first described almost 150 yr ago by Little, an orthopedic surgeon. He suggested that the primary causes included birth trauma and asphyxia, as well as prematurity, and that improved obstetrical care would significantly reduce the incidence of CP. During the last 2–3 decades, there have been considerable advances in obstetric and neonatal care, but, unfortunately, there has been virtually no change in the incidence of CP.

**EPIDEMIOLOGY AND ETIOLOGY.** The Collaborative Perinatal Project, in which approximately 45,000 children were regularly followed from pregnancy to the age of 7 yr, reported the prevalence rate of CP to be 4/1,000 live births. Birth asphyxia was an uncommon cause of CP; moreover, most high-risk pregnancies resulted in neurologically normal children. Although a cause for CP could not be identified in most cases, a substantial number of children with CP had congenital anomalies external to the central nervous system (CNS), which may have placed them at increased risk for developing asphyxia during the perinatal period. An Australian study comparing children with spastic CP with a group of matched controls had similar findings. Less than 10% of children with CP had evidence of intrapartum asphyxia. Although the increased survival of premature infants from improved perinatal care has resulted in more children with CP, the rate did not increase (see Chapter 82). These studies suggest that future developments aimed at enhancing perinatal care will have minimal impact on the incidence of CP and that research might be directed more profitably to the field of developmental biology in order to understand the pathogenesis of CP.

**CLINICAL MANIFESTATIONS.** CP may be classified by a description of the motor handicap in terms of physiologic, topographic, and etiologic categories and functional capacity (Table 548–1). The physiologic classification identifies the major motor abnormality, whereas the topographic taxonomy indicates the involved extremities. CP is also commonly associated with a spectrum of developmental disabilities, including mental retardation, epilepsy, and visual, hearing, speech, cognitive, and behavioral abnormalities. The motor handicap may be the least of the child's problems.

Infants with *spastic hemiplegia* have decreased spontaneous movements on the affected side and show hand preference at a very early age. The arm is often more involved than the leg, and difficulty in hand manipulation is obvious by 1 yr of age. Walking is usually delayed until 18–24 mo, and a circumductive gait is apparent. Examination of the extremities may show growth arrest, particularly in the hand and thumbnail, especially if the contralateral parietal lobe is abnormal, because extremity growth is influenced by this area of the brain. Spasticity is apparent in the affected extremities, particularly the ankle, causing an equinovarus deformity of the foot. The child often walks on tiptoes because of the increased tone, and the affected upper extremity assumes a dystonic posture when the child runs. Ankle clonus and a Babinski sign may be present; the deep tendon reflexes are increased; and weakness of the hand and foot dorsiflexors is evident. About one third of patients with spastic hemiplegia have a seizure disorder that usually develops during the first year or two, and approximately 25% have cognitive abnormalities including mental retardation. A computed tomography (CT) scan or magnetic resonance imaging (MRI) may show an atrophic cerebral hemisphere with a dilated lateral ventricle contralateral to the side of the affected extremities. Intrauterine thromboembolism with focal cerebral infarction may be one etiology; CT or MRI at birth in infants with focal seizures often demonstrates the area of infarction.

*Spastic diplegia* refers to bilateral spasticity of the legs. The first indication of spastic diplegia is often noted when the infant begins to crawl. The child uses the arms in a normal reciprocal fashion but tends to drag the legs behind more as a rudder (commando crawl) rather than using the normal four-stance crawling movement. If the spasticity is severe, the application of a diaper is difficult owing to excessive adduction of the hips. Examination of the child reveals spasticity in the legs with brisk reflexes, ankle clonus, and a bilateral Babinski sign. When the child is suspended by the axillae, a scissoring posture of the lower extremities is maintained. Walking is significantly delayed; the feet are held in a position of equinovarus; and the child walks on tiptoes. Severe spastic diplegia is characterized by disuse atrophy and impaired growth of the lower extremities and by disproportionate growth with normal development of the upper torso. The prognosis for normal intellectual development is excellent for these patients, and the likelihood of seizures is minimal. The most common neuropathologic finding is periventricular leukomalacia, particularly in the area where fibers innervating the legs course through the internal capsule. This lesion is noted among premature infants.

*Spastic quadriplegia* is the most severe form of CP because of marked motor impairment of all extremities and the high association with mental retardation and seizures. Swallowing difficulties are common owing to supranuclear bulbar palsies and often lead to aspiration pneumonia. At autopsy, the central white matter is disrupted by areas of necrotic degeneration that may coalesce into cystic cavities. Neurologic examination shows increased tone and spasticity in all extremities, decreased spontaneous movements, brisk reflexes, and plantar extensor responses. Flexion contractures of the knees and elbows are often present by late childhood. Associated developmental disabilities, including speech and visual abnormalities, are particularly prevalent in this group of children. Children with spastic quadriparesis often have evidence of athetosis and may be classified as mixed CP.

*Athetoid CP* is relatively rare, especially since the advent of aggressive management of hyperbilirubinemia and the prevention of kernicterus. These infants are characteristically hypotonic and have poor head control and marked head lag. Feeding may be difficult, and tongue thrust and drooling may be prominent. The athetoid movements may not become evident until 1 yr of age and tend to coincide with hypermyelination of the basal ganglia, a phenomenon called **status marmoratus.**

■ TABLE 548–1 Various Classification Systems for Cerebral Palsy*

| Physiologic | Topographic | Etiologic | Functional |
|---|---|---|---|
| Spastic | Monoplegia | Prenatal (e.g., infection, metabolic, anoxia, toxic, genetic, infarction) | Class I—no limitation of activity |
| Athetoid | Paraplegia | | |
| Rigid | Hemiplegia | | Class II—slight to moderate limitation |
| Ataxic | Triplegia | | |
| Tremor | Quadriplegia | Perinatal (e.g., anoxia) | Class III—moderate to great limitation |
| Atonic | Diplegia | | |
| Mixed | Double hemiplegia | Postnatal (e.g., toxins, trauma, infection) | Class IV—no useful physical activity |
| Unclassified | | | |

*Adapted from Minear WL: A classification of cerebral palsy. Pediatrics 18:841, 1956.*

Speech is typically affected owing to involvement of the oropharyngeal muscles. Sentences are slurred, and voice modulation is impaired. Generally, upper motor neuron signs are not present, seizures are uncommon, and intellect is preserved in most patients.

**DIAGNOSIS.** A thorough history and physical examination should eliminate a progressive disorder of the CNS, including degenerative diseases, spinal cord tumor, or muscular dystrophy. Depending on the severity and the nature of the neurologic abnormalities, a baseline electroencephalogram (EEG) and CT scan may be indicated to determine the location and extent of structural lesions or associated congenital malformations. Additional studies may include tests of hearing and visual function. As CP is usually associated with a wide spectrum of developmental disorders, a multidisciplinary approach is most helpful in the assessment and management of such children.

**TREATMENT.** A team of physicians from various specialties as well as the occupational and physical therapists, speech pathologist, social worker, educator, and developmental psychologist provide important contributions to the management of the child. Parents should be taught how to handle their child in daily activities such as feeding, carrying, dressing, bathing, and playing in ways that will limit the effects of abnormal muscle tone. They also need to be instructed in the supervision of a series of exercises designed to prevent the development of contractures, especially a tight Achilles tendon. There is no proof that physical or occupational therapy will prevent the development of CP in the infant at risk or that it will correct the neurologic deficit, but there is ample evidence that therapy optimizes the development of the abnormal child. The child with spastic diplegia is treated initially with the assistance of adaptive equipment, such as walkers, poles, and standing frames. If the patient has marked spasticity of the lower extremities or if there is evidence of hip dislocation, consideration should be given to performing surgical soft-tissue procedures that reduce muscle spasm around the hip girdle, including an adductor tenotomy or psoas transfer and release. A rhizotomy procedure in which the roots of the spinal nerves are divided has produced considerable improvement in selected patients with severe spastic diplegia. A tight heel cord in a child with spastic hemiplegia may be treated surgically by tenotomy of the Achilles tendon. The quadriplegic patient is managed with motorized wheelchairs, special feeding devices, modified typewriters, and customized seating arrangements. Communication skills may be enhanced by the use of Bliss symbols, talking typewriters, and specially adapted computers including artificial intelligence computers to augment motor and language function. Significant behavior problems may substantially interfere with the development of a child with CP; their early identification and management are important, and the assistance of the psychologist or psychiatrist may be necessary. Learning and attention deficit disorders and mental retardation are assessed and managed by a psychologist and educator. Strabismus, nystagmus, and optic atrophy are common in children with CP; thus, an ophthalmologist should be included in the initial assessment. Lower urinary tract dysfunction should receive prompt assessment and treatment. Several drugs have been utilized to treat spasticity, including dantrolene sodium, the benzodiazepines, and baclofen. These medications are generally ineffective but should be considered if severe spasticity is not controlled by other measures. Intrathecal baclofen has been used successfully in selected children with severe spasticity. This experimental therapy requires a team approach and constant follow-up for complications of the infusion pumping mechanism and infection. Botulinum toxin is undergoing study for the management of spasticity in specific muscle groups, and the preliminary findings show a positive response in those patients studied. Occasionally, patients with incapacitating athetosis will respond to levodopa, and children with dystonia may benefit from carbamazepine or trihexyphenidyl.

## 548.2 Mitochondrial Encephalomyopathies

At least three associated disorders are characterized by cerebral disease and mitochondrial myopathy and are included in this section devoted to the encephalopathies. Leigh disease and Reye syndrome are discussed here because they result from disorders of mitochondrial function. Further discussion may be found in Chapters 72, 306, and 552.

**MITOCHONDRIAL ENCEPHALOMYOPATHY, LACTIC ACIDOSIS, AND STROKE-LIKE EPISODES* (MELAS).** Patients with MELAS may be normal for the first several years, but gradually they display delayed motor and cognitive developmental milestones. These children develop short stature and either a focal or generalized seizure disorder. Ultimately, the patient presents with an acute hemiparesis that can alternate from side to side. CT studies show basal ganglia calcification in some patients and lucent areas in the cerebral hemispheres. Serum lactate levels during an acute episode are elevated. Muscle biopsies usually, but not always, show ragged-red fibers. MELAS is a progressive disorder that has been reported in siblings. It is punctuated with episodes of hemiparesis, hemianopia, cortical blindness, and progressive dementia secondary to multiple strokes. The location of the lucent lesions noted on the CT scan is compatible with the acute neurologic deficit. Postmortem studies have demonstrated focal encephalomalacia, cortical microcystic liquefaction, and basal ganglia calcifications. The prognosis for patients with the full syndrome is dismal. Therapeutic trials have included corticosteroids and CoQ10. Lowering the serum lactate concentration with dichloroacetate in patients with severe lactic acidosis may result in marked clinical improvement. Most

*Written with the collaboration of Dr. Ingrid Tein.

patients will have a highly specific, although not exclusive, point mutation at nt 3243 in the $tRNA^{Leu}$ (UUR) gene of mtDNA, which has provided an important diagnostic tool. Biochemical studies of muscle have shown complex I deficiency in many patients; however, multiple defects of the respiratory chain, affecting complexes I, III, and especially complex IV, have also been documented.

**MYOCLONUS EPILEPSY AND RAGGED-RED FIBERS (MERRF).** Patients with MERRF may also be normal during the early years of development. However, all patients ultimately develop myoclonic epilepsy and progressive ataxia associated with dysarthria and nystagmus; a few have optic atrophy. Because some patients have abnormalities of deep sensation and pes cavus, the condition may be confused with Friedreich ataxia. Less common signs include dementia, hearing loss, peripheral neuropathy, and spasticity. Intellectual deterioration is slowly progressive in patients with MERRF. As with MELAS, a significant number of patients have a positive family history and short stature. Pathologic findings include elevated serum lactate levels, ragged-red fibers in muscle biopsies, marked loss and degeneration of neurons in the dentate nuclei and the inferior olivary complex with dropout of Purkinje cells and neurons of the red nucleus. The cerebral cortex and white matter are usually normal. Most patients will have a highly specific, although not exclusive, point mutation at nt 8344 in the $tRNA^{Lys}$ gene of mtDNA. There have been inconsistent results in biochemical studies of muscle, including defects of complex III; complexes II and IV; complexes I and IV; complexes I, III, and IV; or complex IV alone.

**KEARNS-SAYRE SYNDROME (KSS).** The criteria for KSS include a triad of (1) onset before age 20 yr, (2) progressive external ophthalmoplegia, and (3) pigmentary retinopathy. There must also be at least one of the following: heart block, cerebellar syndrome, or a cerebrospinal fluid protein above 100 mg/dL. Other nonspecific but common features include dementia, sensorineural hearing loss, and endocrine abnormalities, including short stature, diabetes mellitus, and hypoparathyroidism. The prognosis is poor despite placement of a pacemaker. Ragged-red fibers are found in muscle biopsies with a variable number of COX-negative fibers. Almost all patients have mtDNA deletions. These may be new mutations accounting for the sporadic nature of KSS.

**GENETICS OF DISEASES CAUSED BY DEFECTS OF MITOCHONDRIAL DNA.** Diseases caused by defects of mitochondrial DNA (mtDNA) include deletions and duplications as well as point mutations. In the group of deletions, patients have a single deletion in their mtDNA. This deletion is identical in all tissues in a given patient, although the number of deleted genomes varies from tissue to tissue *(heteroplasmy)*. The three major clinical syndromes in the group of deletions and duplications, in which the inheritance tends to be sporadic, are Kearns-Sayre syndrome, progressive external ophthalmoplegia with ragged-red fibers, and Pearson marrow/pancreas syndrome.

In the group of point mutations, there are four maternally inherited diseases, which include *Leber hereditary optic neuroretinopathy,* MELAS, MERRF, and *ATPase 6 mutation syndrome.* In maternal inheritance, the transmission is maternal but both sexes are equally affected. The phenotypic expression of an mtDNA mutation will be dependent upon the relative proportions of mutant and wild-type genomes among the multiple copies of mtDNA in each cell. There is a minimum critical number of mutant genomes necessary for expression of the disease, and this is known as the *threshold effect.* The proportion of mutants may shift in daughter cells during cell division *(mitotic segregation),* and the phenotype may thereby change. The subsequent generations are affected by a pathologic mutation as in autosomal dominant diseases; however, the number of affected individuals in each generation should be higher than in autosomal dominant diseases. The threshold effect may vary from tissue to tissue depending upon the individual tissue vulnerability to oxidative impairment and may vary in the same tissue with time. The mitochondrial proliferation leading to the formation of ragged-red fibers appears to be triggered by an imbalance between the energy requirement and oxidation/phosphorylation efficiency of the muscle fiber.

**LEIGH DISEASE (SUBACUTE NECROTIZING ENCEPHALOMYELOPATHY).** There are at least three known genetically determined causes of Leigh disease: deficiency of the pyruvate dehydrogenase complex, deficiency of complex I, and deficiency of complex IV of the respiratory chain (see also Chapter 73). These defects may occur sporadically or be inherited by autosomal recessive transmission, as in the case of COX deficiency, or by x-linked transmission, as in PDH $E_1$ alpha deficiency. Most patients present during infancy with feeding and swallowing problems, vomiting, and failure to thrive. Delayed motor and language milestones may be evident, and generalized seizures, weakness, hypotonia, ataxia, tremor, pyramidal signs, and nystagmus are prominent findings. Intermittent respirations with associated sighing or sobbing are characteristic and suggest brain stem dysfunction. Some patients have external ophthalmoplegia, ptosis, optic atrophy, and decreased visual acuity. Abnormal results on CT scans consisting of bilaterally symmetric areas of low attenuation in the basal ganglia have been described in some patients. Pathologic changes consist of focal, symmetric areas of necrosis in the thalamus, basal ganglia, tegmental gray matter, periventricular and periaqueductal regions of the brain stem, and posterior columns of the spinal cord. Microscopically, these *spongiform* lesions show cystic cavitation with neuronal loss, demyelination, and vascular proliferation. Elevated serum lactate levels are the hallmark of Leigh disease. The overall outlook in Leigh disease is poor, but a few patients experience prolonged periods of remission.

**REYE SYNDROME.** This encephalopathy is associated with fatty degeneration of the viscera and a disorder of mitochondrial function (see Chapter 306).

## 548.3 Other Encephalopathies

**ZELLWEGER SYNDROME (CEREBROHEPATORENAL SYNDROME [CHRS]).** This rare, lethal disorder is inherited as an autosomal recessive trait. It represents the prototype of a group of peroxisomal disorders that have overlapping symptoms, signs, and biochemical abnormalities (see Chapter 72.2). Infants with Zellweger syndrome have dysmorphic facies consisting of frontal bossing and a large anterior fontanel. The occiput is flattened, and the external ears are abnormal. A high-arched palate, excessive skin folds of the neck, severe hypotonia, and areflexia are usually evident. Examination of the eyes reveals searching nystagmoid movements, bilateral cataracts, and optic atrophy. Generalized seizures become evident early in life, associated with severe global developmental delay and a significant bilateral hearing loss. Hepatomegaly is a prominent finding shortly after birth, often associated with a history of prolonged neonatal jaundice. Patients with Zellweger syndrome rarely survive beyond 1 yr of age.

**ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS) ENCEPHALOPATHY.** Encephalopathy is an unfortunate and common manifestation of infants and children with human immunodeficiency virus (HIV) infection (see Chapter 223). Neurologic signs in the congenitally infected patient may appear during early infancy or may be delayed to as late as 5 yr of age. The encephalopathy may have an acute onset with a relentless progressive course, but in some cases the process is either static or is characterized by insidious deterioration. The primary features of AIDS encephalopathy include an arrest in brain growth, evidence of developmental delay, and the evolution of neurologic signs.

**LEAD ENCEPHALOPATHY.** See Chapter 665.

**BURN ENCEPHALOPATHY.** An encephalopathy develops in approximately 5% of children with significant burns during the first several weeks of hospitalization (see also Chapter 60.5). There is no single cause of burn encephalopathy but rather a combination of factors that include anoxia (smoke inhalation, carbon monoxide poisoning, laryngospasm), electrolyte abnormalities, bacteremia and sepsis, cortical vein thrombosis, a concomitant head injury, cerebral edema, drug reactions, and emotional distress. Seizures are the most common clinical manifestation of burn encephalopathy, but altered states of consciousness, hallucinations, and coma may also occur. The management of burn encephalopathy is directed to a search for the underlying cause and treatment of hypoxemia, seizures, specific electrolyte abnormalities, or cerebral edema. The prognosis for complete neurologic recovery is generally excellent, particularly if seizures are the primary abnormality.

**HYPERTENSIVE ENCEPHALOPATHY.** Hypertensive encephalopathy is most commonly associated with renal disease in children, including acute glomerulonephritis, chronic pyelonephritis, and end-stage renal disease (see Chapters 404, 481.2). In some cases, hypertensive encephalopathy is the initial manifestation of underlying renal disease. Marked systemic hypertension produces vasoconstriction of the cerebral vessels, which leads to vascular permeability, causing areas of focal cerebral edema and hemorrhage. The onset may be acute, with seizures and coma, or more indolent, with headache, drowsiness and lethargy, nausea and vomiting, blurred vision, transient cortical blindness, and hemiparesis. Examination of the eyegrounds may be normal in children, but papilledema and retinal hemorrhages may occur. Treatment is directed to the restoration of a normotensive state and control of seizures with appropriate anticonvulsants.

**RADIATION ENCEPHALOPATHY.** Although techniques for administering radiation therapy to the brain have improved considerably and the incidence of serious side effects has decreased significantly, radiation encephalopathy remains an important complication. *Acute radiation encephalopathy* is most likely to develop in young patients who have received large daily doses. The excessive radiation injures vessel endothelium, resulting in enhanced vascular permeability, cerebral edema, and multiple hemorrhages. The child may suddenly become irritable and lethargic, complain of headache, or present with focal neurologic signs and seizures. The patient occasionally develops hemiparesis due to an infarct secondary to vascular occlusion of the cerebral vessels. Steroids are often beneficial in reducing the cerebral edema and reversing the neurologic signs. *Late radiation encephalopathy* develops months to years after the completion of therapy. It is rare in children. The condition is characterized by headaches and slowly progressive focal neurologic signs, including hemiparesis and seizures. Although the cause of late radiation encephalopathy is unknown, the CT scan shows cerebral atrophy and low-density lesions. Some children with acute lymphatic leukemia who are treated with a combination of intrathecal methotrexate and cranial irradiation develop neurologic signs months or years later, consisting of increasing lethargy, loss of cognitive abilities, dementia, and focal neurologic signs and seizures (see Chapter 448). The CT scan shows calcifications in the white matter, and the post mortem examination demonstrates a necrotizing encephalopathy. This devastating complication of the treatment of leukemia has prompted a re-evaluation of the use of cranial radiation in the management of these children.

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# CHAPTER 549

## *Coma in Childhood*

Coma is defined as a state of unconsciousness from which the child cannot be aroused by ordinary verbal, sensory, or physical stimuli. Coma is a medical emergency (see Chapter 60.2). Prompt diagnosis and appropriate management may be lifesaving. Treatment often precedes a thorough physical examination. The patient's airway and cardiorespiratory system must be examined immediately, and the vital signs must be recorded. If the patient is in shock or has had a cardiorespiratory arrest, the immediate management is directed to resuscitation and to the establishment of life support systems. Generally, a child with a Glasgow Coma Scale of seven or less should be intubated and placed on a respirator (see later). On the other hand, if the patient's vital signs and cardiovascular system are intact, attention may be directed to the history and physical examination.

The *history* may indicate the cause, but frequently the parent is unavailable or was not present at the onset of the coma. It is important to determine whether there has been a gradual change in personality and behavior or an abrupt loss of con-

sciousness. The amount, type, and time of the last dose of insulin in the diabetic child is important to document. Because intoxication is a prominent cause of coma in the toddler and adolescent patient, a careful review of medications and their location at home should be completed. The discovery of the child in close proximity to the medicine cabinet or storage area or the finding of pills and empty medication containers is overwhelming evidence of drug-induced coma. If there is any doubt about the history, or if the clinical and laboratory findings do not support the history, a home visit may be invaluable. A toxic substance or spilled pills from an opened container may be found within the child's play area. An altered state of consciousness in the newborn period associated with vomiting, failure to thrive, and seizures suggests an inborn error of metabolism. The patient in status epilepticus or in a postictal state following an initial seizure, and the child with a history of chronic renal disease associated with hypertensive encephalopathy may present with coma. A child with severe pulmonary or heart disease or profound anemia may develop coma as a consequence of cerebral anoxia and ischemia. Rarely, brain tumors or cerebral abscess, particularly if there is rupture into the ventricular system, may produce sudden coma. These children may have a history of headache, vomiting, change in personality, or congenital heart disease. Acute subarachnoid hemorrhage secondary to a bleed from an arteriovenous malformation causes a sudden alteration in consciousness.

The child's level of consciousness and the response to stimuli should be carefully documented. A modification of the *Glasgow Coma Scale* in Table 59–5 is a useful tool for the grading of the degree of coma and the severity of the insult in infants and children. It is important to remember that the assessment of the verbal response is much different from that of the adult, and the child's developmental level must be kept in mind during the evaluation. A coma score of less than five is associated with a grave prognosis, whereas a score of five to eight may indicate a better prognosis in the child than in the adult.

The *physical examination* is helpful in distinguishing between a metabolic cause and structural cause for the coma. A slow, irregular pulse combined with systemic hypertension indicates increased intracranial pressure or hypertensive encephalopathy. The rate and rhythm of the respiratory pattern provide useful information about the etiology of the coma. Regular and deep hyperventilation (Kussmaul breathing) indicates metabolic acidosis; subdued and slow breathing suggests respiratory depression or sedation; and irregular, ataxic respiration suggests cerebellar herniation. Cherry-red discoloration of the face and cheeks is associated with carbon monoxide poisoning. A fruity breath is typical of diabetic ketoacidosis; a putrid odor indicates hepatic coma; and a sweet-smelling urine suggests maple syrup urine disease (see Chapter 71.6).

The examination should include a careful search for trauma and should test for the presence of nuchal rigidity. Cerebrospinal fluid (CSF) rhinorrhea, hematotympanum, and **Battle sign** (bruising over the mastoid) are suggestive of a basilar skull fracture. Nuchal rigidity may indicate meningitis, encephalitis, subarachnoid bleed, or herniation of the cerebellar tonsils. Pin-point *pupils* are associated with narcotics, barbiturate toxicity, organophosphates, and phencyclidine. Small and irregular pupils suggest a lesion in the pons, and dilated and unresponsive pupils are seen in the postictal state, with botulism, and with certain drugs, including glutethimide, amphetamine, atropine, cocaine, ethyl alcohol, and mydriatics. A unilaterally dilated and unresponsive pupil in the comatose child indicates herniation of the uncus of the ipsilateral temporal lobe. Check to ensure that a mydriatic was not the cause of the abnormal pupil. The integrity of the extraocular muscles may be tested by the doll's eye maneuver. The fundi must be examined for the presence of papilledema and retinal hemorrhages.

Brain stem function may be evaluated by *ice water* caloric testing (unless the tympanic membrane is ruptured) (see Chapter 541). The comatose child with an intact brain stem shows a fixed deviation of the eyes to the side of the stimulus, and the patient with irreversible coma has no response.

Focal neurologic signs may be difficult to elicit in the comatose patient. *Hemiparesis* may be demonstrated by passively flexing the legs and hips. The examiner suddenly releases the extremities. The hemiparetic leg will rapidly fall to an externally rotated position, whereas the normal limb will slowly slide back to the original posture. This maneuver should be carried out with the patient supine and on a flat surface. The quadriceps may be flattened, and the foot of the affected extremity is externally rotated owing to a decrease in muscle tone. Finally, the hemiparetic extremities may have altered reflexes, changes in muscle tone, and an extensor plantar reflex.

During the initial evaluation an *IV line* is established and blood is obtained for a complete blood count, electrolytes, calcium, phosphorus, glucose, creatinine, blood gases, liver function studies, prothrombin and partial thromboplastin, ammonium level, and a toxic screen. It is important to collect and store an additional 5 mL of heparinized blood that can be utilized later if a specific metabolic disease becomes apparent. Table 549–1 provides a framework to differentiate the various common causes of metabolic coma. If the initial Dextrostix suggests hypoglycemia, 2 mL/kg of 25% dextrose should be given IV. A *urinary catheter* is inserted; the urine volume is noted; and a sample is examined for glucose, ketones, and further studies as indicated. A *nasogastric tube* is placed in position, and the stomach is emptied with care to prevent aspiration, particularly if a toxin is suspected. The stomach contents may be analyzed in the laboratory for specific toxins. Structural causes of coma include concussion, contusion, subdural and epidural hematoma, cerebral edema, brain tumors, and cerebral abscess. The diagnosis and management of these conditions are discussed elsewhere in this section.

The principles of *treatment* include maintenance of the respiratory status, normalization of cardiovascular function, and correction of acid-base, fluid, and electrolyte abnormalities. IV fluids used for resuscitation and infusion should be carefully monitored as hyponatremia, which may aggravate a cerebral injury, is a common complication of IV therapy in the comatose patient. Seizures, increased intracranial pressure, and hyperthermia (or hypothermia) are managed appropriately. The primary goal of treatment is to identify the specific cause of the coma and to correct the problem in a safe and controlled fashion.

The use of **invasive intracranial pressure monitoring** should be considered for any infant or child with nontraumatic coma and suspected increase in intracranial pressure to assess cerebral perfusion and to anticipate shifts in brain tissue. Cerebral perfusion pressure is calculated as the difference between the mean arterial blood pressure and the mean intracranial pressure. Neurologic outcome is improved if the cerebral perfusion pressure can be maintained above 50 mm Hg. Poor neurologic outcome or death is associated with intracranial pressures above 50 mm Hg or cerebral perfusion pressures of less than 40 mm Hg. Intracranial pressure in the child may be monitored by the use of a subarachnoid screw, a subdural pressure transducer, or a fluid-filled intraventricular catheter. Raised intracranial pressure may be lowered by paralysis and sedation with pancuronium, phenobarbital, morphine, or diazepam, mechanical hyperventilation ($Paco_2$ lowered to 30–35 mm Hg), osmotherapy with IV mannitol or furosemide, or drainage of CSF through the ventricular catheter. Too aggressive hyperventilation may further compromise already ischemic areas of the brain. A decrease in cerebral perfusion pressure associated with a low systemic arterial pressure may be enhanced by infusions of colloid or dopamine.

■ TABLE 549–1 Coma in the Pediatric Population: Metabolic Coma

| Etiology | Symptoms and Signs | Diagnosis |
|---|---|---|
| ***Intoxication*** | | |
| Salicylism | Hyperventilation, dehydration, seizures | Metabolic acidosis, ketonuria, urine ferric chloride (burgundy color), increased serum salicylate |
| Barbiturates | Hypoventilation, decreased blood pressure, pin-point pupils | Increased serum phenobarbital level (>30 μg/mL) |
| Alcohol | Respiratory failure, seizures | Serum alcohol: coma = 300–500 mg/dL, >500 mg/dL may be lethal; hypoglycemia |
| ***Hyperglycemia*** | | |
| Diabetes mellitus | Hyperventilation, fruity odor | Glycosuria, ketonuria, ketonemia, metabolic acidosis, hyperosmolality |
| Head injury | External evidence of trauma or focal signs | Glycosuria, no ketonemia or ketonuria |
| ***Hypoglycemia*** | | |
| Insulin excess | Perspiration, pallor, seizures | Blood glucose <40 mg/dL |
| Salicylism | As above | — |
| Alcohol | As above | — |
| ***Inborn Errors*** | Vomiting, changes in tone, seizures | Metabolic acidosis, positive 2,4 dinitrophenyl-hydrazine, increased organic acids, increased amino acids, increased serum lactate |
| ***Electrolyte Abnormalities*** | Hypernatremia, hyponatremia, hypocalcemia, hypokalemia | Serum electrolytes, calcium and magnesium |
| ***Meningoencephalitis*** | Fever, nuchal rigidity, seizures | Examination of CSF; brain scan, EEG, and CT scan if herpes suspected |
| ***Encephalopathy*** | | |
| Anoxic | Cardiac arrest, severe anemia/pulmonary disease | Pulseless, ECG, Hb, chest radiograph |
| Reye syndrome | Hyperpnea, apneic breathing, decerebrate posture, dilated pupils, seizures, combative | Increased serum ammonia, SGOT, SGPT, and prolonged PT, hyperaminoacidemia (lysine and glutamine), characteristic liver biopsy |
| Hypertensive | Renal disease, coarctation of the aorta, collagen vascular disease, pheochromocytoma | Increased blood pressure, retinal changes, decreased femoral pulses, neurofibromatosis? |
| Hemorrhagic shock (HSES) | Malaise, fever, vomiting and diarrhea, seizures, cyanosis | Metabolic acidosis, acute renal failure, increased liver enzymes, anemia, and DIC |
| Hemolytic-uremic syndrome (HUS) | Irritability, pallor, purpura, oliguria, seizures | Decreased Hb, decreased platelets, fragmented red blood cells, hematuria, renal failure, verotoxin-producing *Escherichia coli* |
| Lead | Vomiting, abdominal pain, ataxia, seizures | Blood lead greater than 100 μg/dL |
| ***Postseizure*** | Dilated pupils, Babinski, rapid return of consciousness | Medicalert bracelet? |

The induction of pentobarbital coma and the use of steroids do not appear to influence the neurologic *prognosis* in the comatose child. The prediction of coma outcome during the acute illness depends in part on the etiology of the condition; diabetic ketoacidosis has a more favorable outlook than Reye syndrome, while trauma is more favorable than anoxia. However, certain physical signs provide some indication of outcome before inducing paralysis and placement on the respirator. These signs include severity of the coma (i.e., modified Glasgow score), eye movement, pupil reaction, hypotension, temperature, motor patterns, and the seizure type. The EEG is also useful to estimate the potential for neurologic recovery. For example, the reappearance of normal sleep spindles is an encouraging finding, even if associated with high-voltage slow waves that have no predictive value. EEG patterns associated with a poor prognosis include burst suppression, α-like activity, very low amplitude activity for age, and electrocerebral silence. Neurophysiologic studies have also been used to make a prognosis for comatose children, including brain stem auditory, visual, and somatosensory evoked potentials (SEPs). Generally, the absence of all wave forms in these three modalities is associated with death or severe neurologic residua. Somatosensory evoked potentials are the most sensitive and reliable method for the evaluation of neurologic outcome in the comatose child. If SEPs are recorded early during the course of coma and repeated within the first week, normal SEPs predict normal outcome in 93% of the cases and absent SEPs predict poor outcome in 100% of the cases; asymmetrical SEPs are typically associated with sequelae such as hemiparesis.

# CHAPTER 550
## *Brain Death*

See also Chapter 3.

The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research commented that "Death is defined as irreversible cessation of circulatory and respiratory functions or irreversible cessation of all functions of the entire brain, including the brain stem. A determination of death must be made in accordance with accepted medical standards." The criteria for establishing brain death are similar for adults and children; however, the period of observation may be longer in the latter. The diagnosis of brain death is established when the cause of coma is determined; the possibility for recovery of any brain function is excluded; and the cessation of all brain functions are documented for an appropriate period of observation or trial of therapy. The diagnosis of brain death is made primarily by clinical methods, irrespective of the age of the patient. The physical examination criteria are as follows: (1) the patient must be comatose, apneic, normothermic, and normotensive with absence of vocalization and volitional movement. Apnea is defined as an absence of spontaneous respirations despite an