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Cerebral Edema and Intracranial Dynamics

Monitoring and Management of Intracranial Pressure

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INTRODUCTION

Elevated intracranial pressure (ICP) is a relatively common clinical problem, potentially encountered daily in any neurocritical care unit. Intracranial hypertension can be a hyperacute emergency that must be reversed if profound morbidity or death are to be avoided. The astute clinician can improve patients' outcomes if judicious steps are taken at the right time *(1)*. There have been many advances in our understanding of the physiology of intracranial dynamics. Although our armamentarium remains fairly limited, we may begin to envision its use on a rational, pathophysiologically grounded basis. Unfortunately, too little is yet known to predict exactly which interventions will be effective in exactly which disease states exactly when. Owing in part to the limits of our current technology, but also to a regrettable dearth of clinical trials in the field, current clinical practice is based on a conceptual understanding of underlying pathophysiology but backed by insufficient systematic research with patients. Practice is inevitably the product of the idiosyncratic experience of each individual intensivist. There are insufficient hard data to guide those in the process of gaining that experience.

The goal of this chapter is to first provide an overview of our models of pathophysiology, then to highlight their application in the management of deranged intracranial dynamics. Those few circumstances in which we have objective clinical trial data to guide patient management will be highlighted.

PATHOPHYSIOLOGY

Intracranial Elastance

In all normal humans whose cranial fontanelles have closed, the intracranial contents—brain, blood, and cerebrospinal fluid (CSF)—are encased in a rigid skull; in infants and others with incomplete closure of the calvaria, cerebral expansion is limited by the fibrous dura. In the average adult male, the skull encloses a volume of approx 1450 mL: 1300 mL of brain, 65 mL of CSF, and 110 mL of blood *(2)*.

The Monro-Kellie doctrine dictates these anatomists' observation that the volume of the cranial vault is unchangeable—any process which adds volume to this system must therefore displace volume from elsewhere in the system. Which of the above components is displaced to accommodate extra volume will be considered below. Initially, there is minimal resistance to this displacement. When the limits of displaceability are reached, however, further addition encounters resistance, and this addition must be "squeezed" into the rigid container. This quickly results in an increase in the

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pressure within the system, i.e., raised ICP, which normally ranges between 5 and 15 mmHg (7.5 and 20 cm H_2O). This relationship of ICP to increasing volume of intracranial contents (in one experimental paradigm, an expanding subdural balloon) *(3)* can be expressed as a graph (Fig. 1). This model is just a model, and the pressure-volume curve it generates differs in some respects from that produced by other pathophysiological processes *(4)*, but the basic shape of the curve assumes an increasingly upsloping form in all cases. The slope represents the change in pressure produced by a given change in volume: $\Delta P/\Delta V$, termed "elastance." Initially, with low added volumes, CSF and venous blood are highly displaceable, and pressure rises little; elastance is low. With sufficient added volume, however, compensatory fluid shifts meet with increasing resistance, and pressure rises more and more precipitously—elastance rises. A simple analogy can be made to an elastic band: initial stretch on the band elicits little tensile resistance, but with increasing displacement (stretch), the elastic exerts greater and greater resistance. Likewise, with increasing addition of intracranial displacement (volume), the intracranial contents exert greater force (pressure), resisting further addition.

For semantic and historical reasons, most clinicians describe the status of the intracranial system in terms of $\Delta V/\Delta P$, "compliance," the inverse of elastance: a system which will accommodate significant changes in volume with little increase in pressure has high compliance (because it exerts little elastic resistance, i.e., has low elastance), whereas a system which has exhausted its compensating mechanisms can accommodate little additional volume without large changes in pressure has low compliance (increased elastance).

The Brain

The brain is a viscoelastic solid. It can be displaced to moderate degrees to accommodate an expanding mass. Slowly expanding masses can reach substantial sizes before becoming symptomatic, provided they are not primarily destructive of brain parenchyma, even if they encroach on structurally susceptible locations, such as the tentorial incisura or the foramen magnum *(5)*. The brain's inherent elastic properties generate pressure gradients in such situations *(6,7)*—gradients of up to 20 mmHg across as little as 2 cm of white matter have been reported *(8)*, and ICP is therefore not always uniform *(9)*. Brain is thus one source of intracranial elastance. Its inherent elastic properties can be modulated by changes in brain composition (*see* Brain Water/Brain Edema section) or by the addition of mass effect to the brain parenchyma (e.g., tumor, abscess).

While the glycoproteolipid matrix of the brain produces its structural integrity and elastic properties, the brain remains approx 80% water *(10,11)*, in two compartments. The extracellular compartment represents approx 15% of brain water *(10,11)*, and is in communication with the CSF space (as evidenced by edema bulk flow); the intracellular space comprises the other 85%. It is commonly held that neither of these spaces is appreciably compressible, with moderate direct evidence at best *(11)*. It is clear that either or both these spaces can expand in different disease states (*see* Brain Water/Brain Edema section). Such expansion leads, in effect, to an expansion of the volume of the brain. If such expansion overwhelms volume-compensatory mechanisms, ICP rises.

Brain, then, is minimally compressible, minimally displaceable, and can in some circumstances expand. Venous blood and CSF, by contrast, are much more displaceable, and represent the compensatory mechanisms for increased intracranial volume.

CSF

CSF buoys the brain and cushions it. It is produced as a modulated ultrafiltrate of plasma, with tight control of electrolyte and protein content. Most (80–90%) of its production is at the choroid plexus, with the remainder at the brain capillaries as brain interstitial fluid *(10–12)*. Roughly 500 cc is produced and resorbed each day *(13)*. Resorption occurs at the arachnoid villi into the cerebral venous sinuses (superior sagittal and transverse) by a mechanism that remains poorly understood *(14)*. Produc-

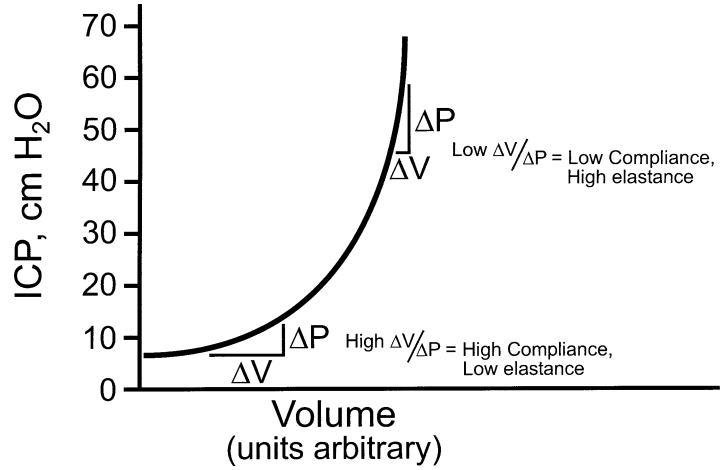

Fig. 1. Intracranial pressure-volume curve. An idealized graph of ICP vs an increasing volume of added mass effect. With increasing added volumes, compensatory mechanisms of the intracranial system are overwhelmed, and ICP becomes increasingly elevated. When compliance is low, small changes in the volume of intracranial tissue (e.g., blood) can precipitate large changes in ICP.

tion is virtually linear, falling off by a trivial amount with increasing ICP *(15)*. The rate at which CSF is resorbed, however, is tightly yoked to ICP: resorption is negligible below an ICP of 6.8 mmHg, and linear above that *(13)*. CSF overproduction, therefore, is very rarely a source of raised ICP.

A pressure gradient is consistently found from the subarachnoid space to cerebral sinus lumina, regardless of the organism's position (upright, supine, Trendelenberg), with a slightly lower pressure in the venous sinuses *(16)*. Venous obstruction, leading to increased venous pressure, increases subarachnoid pressure and thence ICP *(16)*. This has led to the presumption that impaired CSF absorption frequently plays a role in elevated ICP (a presumption with some conceptual justification, discussed in Fig. 4 and The Intracranial System section); however, because the mechanism of CSF absorption is not yet understood, this cannot be considered proven.

In contrast to brain, CSF is readily displaceable from the intracranial compartment, through the foramen magnum and into the lumbar cistern, in compensation for addition of volume elsewhere *(7)*. ICP compensation is profoundly compromised if this route is blocked—in one experimental model by an epidural balloon *(7)*, in some pathological states by tonsillar herniation *(3)*, or in cervical spondylosis by spinal epidural block *(17,18)*.

Of the three states of matter, fluid conveys pressure most effectively. CSF conveys pressure throughout the intracranial and spinal intradural space, as hydrostatic pressure. CSF conveys fluid pressure throughout the intracranial space, moderating the degree to which the brain parenchyma can produce compartmental gradients. Upright posture, by shifting fluid out of the head through the foramen magnum, decreases intracranial pressure and increases lumbar; Trendelenberg does vice versa *(17)*.

CSF, then, is of crucial consequence in states of ICP derangement. Unimpaired resorption likely plays a crucial role in ICP regulation. Maintenance of normal spinal shunting routes is vital to the normal ICP buffering mechanism. Head-up positioning (discussed in the Patient Positioning section) takes advantage of this principle. Direct drainage of CSF (discussed in the CSF Drainage section) can substantially reduce ICP.

Blood

Arterial Blood Flow

Regulation of arterial blood flow in the brain is accomplished by adjustment of the caliber of arterioles—narrow arteries and arterioles admit less blood. Arterial caliber adjusts spontaneously in response to several parameters: systemic arterial pressure, partial pressure of oxygen (pO_2), and partial pressure of carbon dioxide (pCO_2), among others.

At a fixed mean arterial pressure (MAP), cerebral blood flow (CBF) varies nearly linearly with pCO_2 values between 20 and 80 mmHg; this variation produces a change in cerebral blood volume (CBV) of 0.04 mL/100 g brain/mmHgCO_2. With a change in pCO_2 from 40 to 30, a 1200-g brain would see a 4.8-cc decrease in arterial blood volume. Through the normal physiologic range of pO_2, by contrast, CBF is constant. However, with a fall in pO_2 below 50 mmHg, CBF (and hence, CBV) increases rapidly.

Responses to pO_2 and pCO_2 are independent of ICP. Hence, either hypercarbia or hypoxia can dramatically exacerbate intracranial hypertension by further adding arterial blood volume to the intracranial compartment *(3)*. The 4.8-cc change in cerebral volume mentioned above can produce a change in ICP from 20 to 40 mmHg in a patient with decreased compliance. By contrast, however, hypocarbia can be utilized to decrease CBV and hence decrease ICP—either by spontaneous or therapeutic hyperventilation (a technique with limitations, as discussed in the Hyperventilation section).

With gas pressures held constant, CBV remains steady through a wide range of systemic MAP, from approx 50 to 150 mmHg (*see also* Chapter 3). With MAPs above this range of "autoregulation," arterial regulatory mechanisms are overwhelmed and CBV "forcibly" increased (as occurs in malignant hypertension, discussed below); MAPs below this range produce ischemia. Autoregulation does not change in direct response to raised ICP—rather, autonomic responses raise MAP (with a reflex bradycardia, the Cushing response). In many neurologic disease processes (e.g., severe head trauma, ischemia, status epilepticus) the autoregulatory mechanism itself fails, and blood flow becomes roughly linear relative to MAP. Departure from normotension in these circumstances can have profound effects on brain perfusion and CBV.

Systemic blood pressure must be maintained at a sufficient level to provide adequate perfusion to the brain. This dependency is abstracted through the concept of "cerebral perfusion pressure" (CPP), which depends on intracranial pressure and systemic BP through a fundamental relationship:

$$CPP = MAP - ICP$$

where MAP = mean arterial pressure: (1/3 · systolic BP) + (2/3 · diastolic BP). With typical MAPs of 75–90 and ICPs of 5–15, cerebral perfusion is rarely threatened in health. Syncope results when systemic pressure falls to levels insufficient to maintain CPP. With elevation of ICP, MAP must increase to maintain CPP (the Cushing response). If the cardiovascular system cannot produce a sufficient increase in blood pressure, ischemia ensues.

Arterial blood flow and blood volume are thus tightly yoked to physiologic parameters *other* than ICP, and cerebrovascular autoregulatory responses therefore have the capacity to produce intracranial hypertension in conditions of reduced compliance. It is intuitively easy to picture the vicious spiral: if a pathologic process produces decreased intracranial compliance and also threatens CPP, arterial dilation to preserve CPP will also produce a further increase in CBV, which will thereby add to the volume of an intracranial system with decreased compliance, further increasing ICP, necessitating *further* vasodilation to preserve CPP... it is possible that such a mechanism underlies paroxysmal elevations in ICP known as plateau waves (*see* A Waves section). The parameters which control CBF (pO_2, pCO_2, and MAP) must therefore be carefully attended to in patients with deranged intracranial dynamics (*see* the General Cardiopulmonary and Metabolic Support section).

Capillary Blood Flow

Capillary blood volume is difficult to study, and little attention has been paid in the literature to its role in intracranial volume and pressure.

Venous Blood Flow

Cerebral veins are significantly distensible. Evacuation of cerebral and dural venous sinus blood is thought to represent another volume-shifting pressure compensatory mechanism, similar to CSF. The postulated mechanism is intuitively obvious: shunt out of head and into the central venous pool. Direct evidence, however, is less clear for the case of venous blood shift than for CSF shift. It is clear that increased resistance to venous drainage, with elevation of venous pressure, will raise ICP *(16)*; whether the mechanism is impaired CSF resorption or intracranial venous hypervolemia has not yet been clarified. Whether increasing the intrathoracic pressure by positive-pressure ventilation retards cerebral venous drainage is also as yet unclear *(16,19)*.

Venous blood shunting may thus represent the second compensatory mechanism for elevated ICP. What is clear is that venous drainage must not be obstructed in patients with deranged intracranial dynamics (*see* the Patient Positioning section).

Brain Water/Brain Edema

Intracranial fluid can be conceptualized as divided into the same three spaces as in any other tissue of the body—intravascular, interstitial, and intracellular—with the elaboration that the brain contains a specialized compartment of interstitial fluid, the CSF. Proper regulation of brain fluid requires preserved integrity of the barriers between each fluid space; the most crucial and best studied of these barriers is the blood–brain barrier.

Barrier to Intravascular–Interstitial Flow: The Blood–Brain Barrier

Somatic capillary walls can be divided into three main categories—continuous, fenestrated, and sinusoidal *(21,22)*. Sinusoidal capillaries, found in spleen and marrow, contain wide unobstructed openings between endothelial cells to foster maximal exchange of cellular and proteinaceous elements between blood and tissue. Fenestrated capillaries, found in kidney and intestine, have narrower interendothelial spaces that contain a membrane which more tightly controls the plasma constituents allowed out of the vessel. Continuous capillaries, found in brain, nerve, skeletal muscle, heart, and lung, have no spaces between endothelial cells. This permits maximal control over which plasma constituents are permitted into the abluminal tissue.

Brain vasculature is highly restrictive of transendothelial molecular passage. It is this restrictiveness that has been dubbed the blood–brain barrier (BBB). Interendothelial tight junctions in brain capillary are amongst the most highly redoubled in the body *(20)*. They bind adjacent endothelial cells extremely tightly, leaving virtually no space between the cell membranes *(20,22)*. Because of the lack of space between endothelia, passive diffusion across the capillary wall is limited to gases and highly lipophilic substances, which can dissolve directly across the plasmalemmal lipid bilayer. Unlike in virtually every other tissue of the body, there is little to no fluid phase transfer across the endothelium via pinocytotic vesicles *(22–24)*. The only remaining mechanism for traversing the capillary wall, then, is carrier proteins and channels, which in the brain are highly selective to specific metabolites and compounds *(25)*. Endothelial cells in brain capillary contain a very high number of mitochondria *(23)*, suggesting that the functions necessary to maintain the BBB are highly energy-dependent. This barrier, however, is susceptible to opening by various inflammatory mediators, as well as by mechanical, traumatic and pharmacologic mechanisms (*see* Vasogenic Edema and the Starling Equation section).

Barrier to Intravascular–CSF Flow: The Choroid

For reasons of brevity, the complex electrochemical function of the choroid epithelium will not be discussed here. As mentioned previously, the choroid produces approx 80–90% of the CSF, which totals approx 500 cc/d, and rarely is overproduction as source of deranged intracranial dynamics. As discussed in the Acetazolamide section, carbonic anhydrase inhibition can decrease the rate of CSF production at the choroid, but in few pathologic states is this sufficient to ameliorate the derangement in ICP.

Barrier to Interstitial–Intracellular Flow: The Glia

Regulation of brain intracellular space volume is largely the responsibility of glial cells, as they represent the bulk of brain volume. Glial cell processes extend from the ependyma to the subarachnoid glia limitans, and encircle brain capillaries at every level between. It is now appreciated that glia may serve to traffic brain water from each of these locations to others. Recent work has demonstrated that water crosses lipid bilayer membranes in all tissues via a class of membrane channels collectively termed "aquaporins" *(26)*. Only one isoform, AQP-4, is expressed in brain parenchyma. The protein is highly concentrated at astrocytic pericapillary endfeet, and astrocytic processes in contact with subarachnoid and ventricular CSF. The intuitively obvious conjecture is that astroglia play a role in fluid homeostasis that involves conveying water between each of these three surfaces. Manley et al. *(27)* have demonstrated that AQP-4 knockout mice, which demonstrate no neurologic disturbances at baseline, have a dramatically reduced rate of mortality in a systemic hyponatremia model, and have substantially less CNS dysfunction in an MCA stroke model. Other studies have shown differential expression of AQP-4 in models of cerebral ischemia *(28)* and traumatic brain injury *(29)*. Much work remains to be done to clarify the dynamics of water flux through glia, and whether this system might be amenable to pharmacologic intervention in states of deranged intracranial fluid dynamics.

Mechanisms of Brain Edema Formation

Brain edema can be defined as "an abnormal accumulation of fluid within the brain parenchyma producing a volumetric enlargement of the brain tissue" *(30)*. As mentioned previously, swelling of brain tissue alone, if of sufficient magnitude, can displace enough CSF and blood to produce elevated ICP. Alternatively, a mass lesion of modest size can produce dramatic effect on ICP if it produces sufficient surrounding edema.

Brain edema results from accumulation of excess water in either the interstitial compartment, the intracellular compartment, or both. Klatzo *(31)* first promulgated an explicit dichotomy between interstitial vs intracellular fluid accumulation. Arguing that interstitial fluid accumulation results from increased blood vessel wall permeability, Klatzo labeled extracellular edema "vasogenic type." By contrast, he argued, intracellular fluid accumulation resulted from injury to the brain parenchyma itself, with normal vascular permeability; he therefore termed intracellular edema "cytotoxic type." This conceptual dichotomy between cytotoxic and vasogenic edema has been widely adopted. As will be discussed, the putative underlying mechanisms of fluid accumulation in each compartment is not so simple as then thought. Factors other than increased vascular permeability or brain parenchymal injury can result in abnormal amounts of water in each tissue space. Many of the pathologic states leading to brain edema actually exhibit both forms of edema to varying degrees. For these reasons the terms "cytotoxic edema" and "vasogenic edema" are overly reductionistic; however, owing to their universal utilization, this chapter maintains the conventional terminology (Fig. 2).

Vasogenic Edema and the Starling Equation

Accumulation of fluid in the interstitial space can be produced by derangement of the BBB. Flow of water from the intravascular to interstitial space can be modeled in all tissues by the Starling equation:

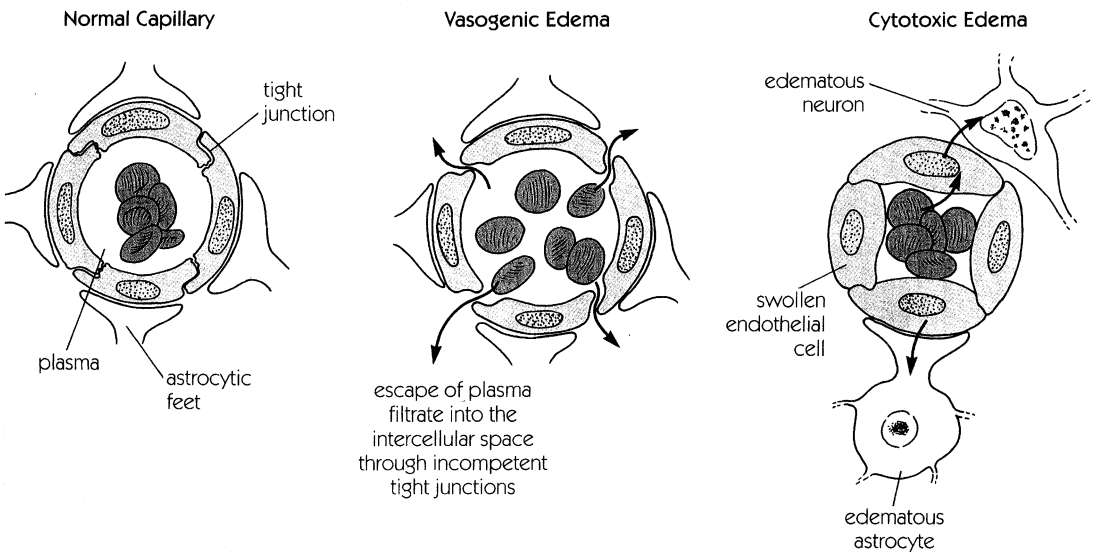

Fig. 2. Mechanisms of edema. This schematic illustrates the traditional conceptualization of brain edema mechanisms. At the capillary wall in normal brain, tight junctions retain protein-rich serum within the capillary. Vasogenic edema develops when tight junction maintenance is deranged, and protein-fluid leaks into the interstitium, drawing free water along with it. Cytotoxic edema develops when cellular energy metabolic failure leads to increased intracellular sodium, free water follows, and tissue swells as its cells take on water. Reprinted from Rengachary SS, Wilkins RA (eds.). Principles of Neurosurgery. London: Wolfe Pub Ltd., 1994, with permission.

$$\text{Fluid movement} = Lp(P_c - P_i) + \Sigma\sigma(\pi_i - \pi_c)$$

where:
L_p = capillary wall hydraulic conductivity;
P_c = hydrostatic pressure in the capillary;
P_i = hydrostatic pressure in the interstitium;
σ = reflection coefficient of the capillary wall for each solute;
π_c = oncotic pressure for each solute within the capillary; and
π_i = oncotic pressure for each solute in the interstitium *(30,32)*.

The first term, $Lp(P_c - P_i)$, reflects the contribution of hydrostatic pressure—that which one usually thinks of when referring to "blood pressure." Virtually always higher in vasculature than tissue, this hydraulic pressure will favor flow of water into tissue. In the brain, this gradient is held in check by the endothelial wall's impermeability to water—a very low Lp. Elevation of intravascular pressure (P_c), decrease in tissue pressure (P_i), or increased conductance of water through the vessel wall (Lp) will all favor increased accumulation of interstitial water—vasogenic edema *(30)*.

Multiple inflammatory mediator—have been implicated in increasing Lp—among them bradykinin, serotonin, histamine, adenine nucleotides (ATP, ADP and AMP), platelet aggregating factor, arachidonic acid, prostaglandins, leukotrienes, IL-1α, IL-1β, IL-2, macrophage inflammatory proteins MIP-1 and MIP-2, complement-derived C3a-desArg, nitric oxide, free radicals *(20,22,23)*, and thrombin *(33)*. The specific role of each of these systems in specific pathological processes is not yet known *(21)*. It is thought that the final common pathway is opening of endothelial tight junctions *(24)*, putatively through calcium-modulated endothelial cell contraction *(21)*, with a resulting profound increase in Lp. There does not appear to be an increase in pinocytosis across endothelium *(21,24)* underlying increased Lp. The role of inflammatory mediators such as nitric oxide and leukotrienes (metabolites of arachidonic acid) is controversial—it is unclear whether they are mediators of opening, or markers of a

process that leads to opening *(21)*. Opening of tight junctions may also be provoked by intravascular osmolarity derangement (π_c) *(24)*, or acute elevation of intravascular pressure (P_c) *(34)*.

The second term in the above equation, $\Sigma\sigma(\pi_i - \pi_c)$, represents the contribution of oncotic (i.e., osmotic) pressure. Due to the normally low Lp of the brain capillary, therefore, most fluid shifts in health are a result of oncotic forces *(10,11)*. Only solutes that have an appreciable concentration gradient ($\pi_i - \pi_c$) across the capillary wall have the potential to create an osmotic gradient; whether they do depends on the capillary wall's permeability to each solute. A solute to which the wall is freely permeable will cross the wall along its gradient and produce no osmotic pressure; this is represented by a σ near zero. A solute with a σ near 1, by contrast (for example, sodium and mannitol), will produce a substantial osmotic gradient if its π_i and π_c are unequal. The net osmotic gradient is the sum (Σ) of the gradient of each individual solute.

Vasogenic edema, then, can be understood in terms of the different constituents of the Starling equation. If tight junctions open, Lp increases, and the magnitude of the first term increases substantially, favoring flow into interstitium. If gap junctions remain open long enough for plasma proteins such as albumin to leak into the interstitium, π_i will be increased by elevated interstitial protein load, further favoring water accumulation. If interstitial edema is to be avoided, the BBB must remain intact.

Once formed, vasogenic edema clears by "sinking" into the CSF *(35,36)*, following a pressure gradient from the edematous brain to CSF space *(37)*. It has been suggested without evidence that that flow takes place along perivascular spaces *(11,35)*; the degree of resistance (at pial-glial interface and at ependymal surface) to that movement is unclear *(11)*.

Obstructive Hydrocephalus

One other mechanism exists by which excess fluid can accumulate in the interstitial space. CSF normally proceeds from the choroid, where it is produced, to the subarachnoid space, where it is resorbed, via the ventricular system. With obstruction of the ventricular system anywhere between the lateral ventricle and the foramina of the fourth ventricle, the only alternate route for CSF to flow is across the brain parenchyma. When this occurs, flow is through the same space that vasogenic edema utilizes in its route from parenchyma into the CSF. This source of excess interstitial fluid differs pathophysiologically from that described above, leading many authors to use the term *interstitial edema* to make the pathophysiologic distinction *(38,39)*. The pressure gradient necessary to force the full volume of ventricular CSF flow across brain parenchyma instead of through the cerebral aqueduct produces profound derangements in brain function; sudden and complete obstruction of the system, as in the ball-valve mechanism of a foramen of Monro colloid cyst, produce a sufficient pressure gradient that cerebral circulatory arrest and death can occur. CSF diversion procedures are done to prevent this gradient of CSF pressure across the brain (*see* CSF Drainage section).

Cytotoxic Edema, Cell Energy Metabolism, and Cellular Fluid Balance

Most discussions of cytotoxic edema cite failure of the Na-K ATPase pump due to shortage of ATP, the putative mechanism being accumulation of intracellular sodium with resulting cell swelling. The name was initially chosen to highlight the presumption that disruption of cellular metabolism was the underlying cause *(31)*. Ischemic stroke is the typical prototype offered.

Brain parenchyma is capable of resisting intravascular osmotic pressure changes; this is largely a function of glia *(11)*. Evidence indicates that mammalian cells utilize small organic molecules, collectively known as organic osmolytes, to regulate the transmembrane osmotic gradient *(40)*. These include polyols such as sorbitol, amino acids such as alanine and taurine, and methylamines such as glycerophosphoral choline. Drop in interstitial osmotic pressure (P_i) results in a flux of these osmolytes out of the cell to drop intracellular osmolarity and maintain water balance. Outward flux of these osmolytes to prevent cell swelling requires expression of an ATP-dependent membrane channel. This provides a conceptual explanation for cell swelling in circumstances of impaired cellular

energy metabolism—cell protein manufacture is impaired in conditions of inadequate ATP, and the function of those channels which are present is impaired by the absence of ATP. Direct evidence for this mechanism in vivo, however, is as yet lacking.

Unlike vasogenic edema, excess intracellular water cannot "sink" into the CSF. Resolution of cytotoxic edema depends upon resolution of the inciting factor. Cells not irreversibly injured will revert to their premorbid state.

Osmotic Edema

Systemic hyponatremia of sufficient severity can also bring about the accumulation of intracellular water by overwhelming cells' capability to accommodate to the hypotonic extracellular environment. In Klatzo's original dichotomy, this is cellular swelling, and hence "cytotoxic" edema. Finding the implication that water is a "toxin" problematic, some authors *(39)* have labeled hyponatremia-induced intracellular edema "osmotic edema" to distinguish it from cytotoxic edema.

Dynamics of ICP

Many processes that lead to accumulation of excess brain water can produce sufficient mass effect that intracranial hypertension ensues. ICP is not monolithic, however; in both pathology and health, ICP is highly variable. Some particular patterns of change, however, are characteristic of pathology.

Cardiac Waves

Intracranial pressure pulses with each pressure wave from the heart—as any neurosurgeon can attest, the brain pulsates. The normal cardiac pressure wave contains three consecutive peaks, in descending order of magnitude: P1 (percussion wave), P2 (tidal wave), and P3 (dicrotic wave) *(10)*. With increased ICP or decreased intracranial compliance, P2 increases in magnitude and P1 becomes blunted; merging of P1 into P2 is one clinical means of detecting declining compliance *(10)*.

Pulmonary Waves

A low-amplitude variation in ICP can also be detected in response to the cycle of intrathoracic pressure (Fig. 3).

A Waves

First demonstrated by Lundberg *(41)*, plateau waves (now commonly referred to as Lundberg A waves) are considered essentially pathognomonic of intracranial hypertension. A waves are sustained (5–20 min), high amplitude (50–100 mmHg) increases in ICP (*see* Fig. 3). Typically exhibited in patients with decreased intracranial compliance, they have however been observed in healthy individuals. Provoked by mental or physical activity, pain, or sleep, they often produce headache, restlessness, confusion, nausea, vomiting, or hyperventilation, but they may be asymptomatic *(41)*. The danger of a plateau wave is the potential for abolishment of the CPP (as previously discussed); sustained A waves can produce global ischemic injury or death. The likely (but unproven) *(42,43)* pathophysiology is arterial vasodilation to compensate for a drop in systemic arterial pressure, with a resulting increase in CBV causing a further increase in ICP—the vicious spiral previously alluded to in the section on Arterial blood flow. Plateau waves of sufficient severity and duration to produce global cerebral ischemia must be reversed, or "broken"—the usual steps undertaken to do so are CSF drainage, hyperventilation, and boluses of osmotic diuretics, to be discussed.

B and C Waves

Other periodic oscillations in ICP were also described by Lundberg, but are of much lesser pathologic consequence. B waves last 1–2 min, are of 20–50 mmHg in amplitude, and are frequently seen in normals, especially in sleep (*see* Fig. 3) *(41)*. C waves last 4–5 min, are less than 20 mmHg, are of no pathologic consequence, and likely represent ICP extension of Traube-Hering vasomotor waves, a poorly understood cyclic variation in systemic BP *(10)*.

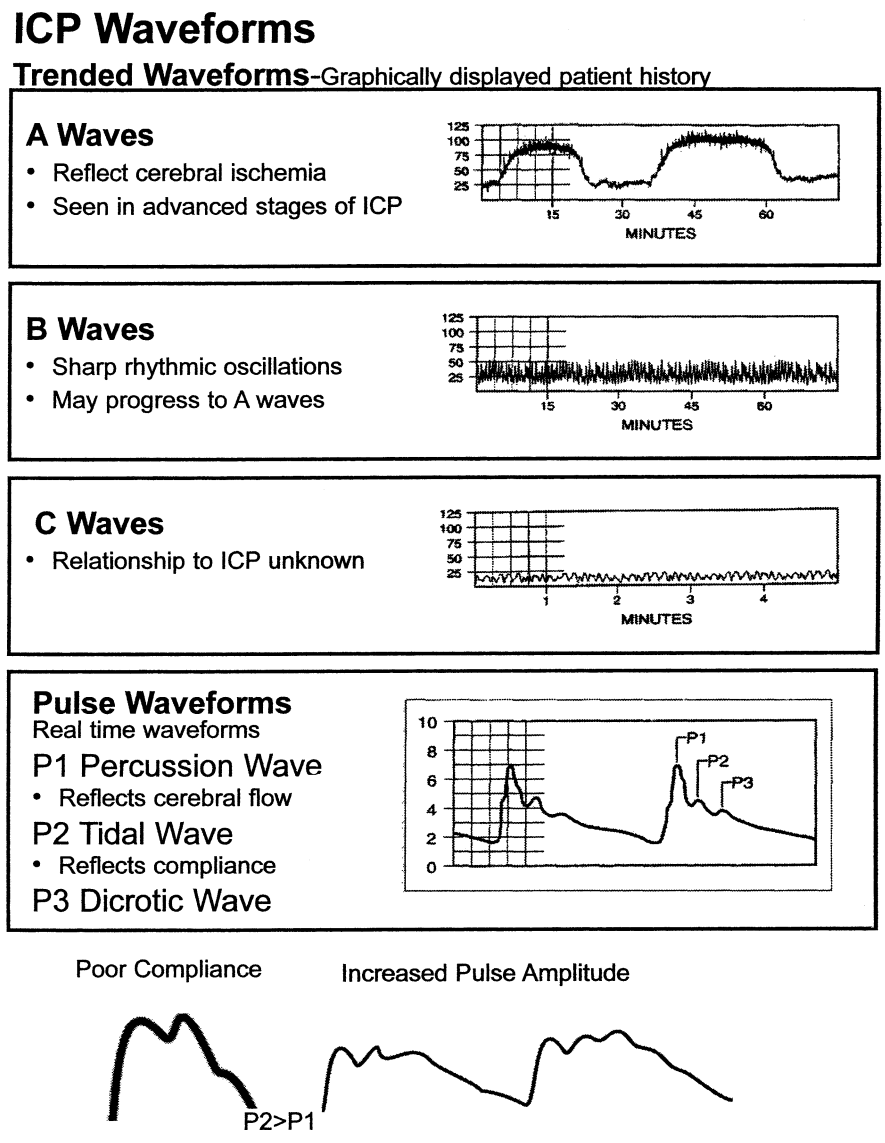

Fig. 3. Intracranial pressure monitoring. A waves are long-duration, sustained elevations of ICP of very high magnitude, sufficient to jeopardize CPP. B waves are of moderate magnitude, and C waves are of low magnitude; both are of short duration, and their pathologic significance is uncertain. CSF pressure monitors also transduce pulsations resulting from arterial blood pressure, and pulse waveforms can be studied for early signs of decreasing compliance—when the initial systolic wave (P1) is blunted and the tidal wave (P2) increased in amplitude, compliance is likely decreased, and the clinician should be alert for the development of A waves. Reprinted from ref. *10* and Integra Neurosciences with permission.

The Intracranial System

Intracranial pressure, then, is a function of the interaction between venous and arterial CBV and CBF, the production, resorption and redistributability of the CSF, the resistance of the brain to stretch, and the presence or absence of additional mass effect such as a tumor, hematoma or abscess. The exact shape of the P/V curve for a particular patient is a complex function of each of these variables. Computer models of the intracranial system *(44–46)* using differential equations to describe each of

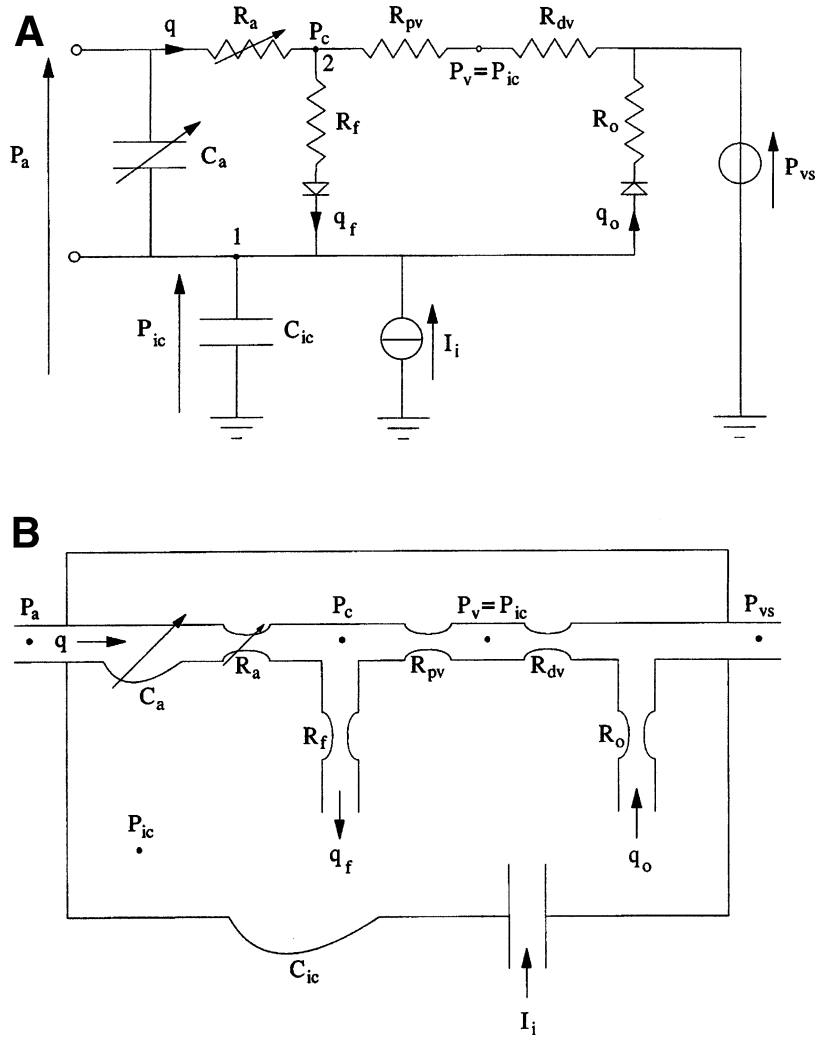

Fig. 4. Electrical (A) and mechanical (B) models of the intracranial system. Cerebral blood volume (q) enters the intracranial space under arterial pressure (P_a). Arterial tone regulates arterial blood volume (C_a) and resistance to its flow (R_a) into the capillaries (P_c). Capillary walls and choroids plexus maintain resistance to the filtration of CSF (Rf) from capillary blood, with a steady flow of CSF (q_f) resulting. Cerebral veins have an intrinsic resistance to blood flow both proximally (R_{pv}) and distally (R_{dv}) en route to the venous sinuses (P_{vs}). Rate of CSF resorption (q_o) depends on the resistance of the arachnoid granulations (R_o). Overall intracranial capacitance (C_{ic}) is an independent function of the fluid spaces; intracranial pressure (P_{ic}) is the net result and an interdependent function of all of the above. (The model also includes an inlet for experimental infusion of artificial CSF, Ii.) This model has a demonstrated ability to reproduce physiologic phenomena of deranged ICP, in particular A waves. Chief among its insights thus far are an increase in resistance to CSF resorption (R_o) in many states of elevated ICP, and the necessity of inclusion of the two separate venous resistances to accurately model ICP dynamics. Although this model has yet to be applied to real patients in real time, it provides conceptual support for the use of CSF drainage to overcome increased R_o, and its existence is reason to hope for rational approaches at some point in the future. Reprinted from ref. *45* with permission.

these factors, with parameters derived from clinical data and animal models, have achieved a remarkable ability to reproduce the behavior of the intracranial system—in particular, the most crucial clinical phenomenon of elevated ICP, A waves (Fig. 4). One of the most striking insights obtained from this model is its support of the association between increased resistance to CSF resorption (R_o) and elevations in ICP, a finding clinically confirmed by the utility of CSF drainage in controlling intracranial hypertension (*see* CSF Drainage section). It will likely be some time, unfortunately, before work on these models has proceeded to the point where they can predict ICP phenomena in individual patients.

ETIOLOGIES OF EDEMA AND RAISED ICP

Any process with the potential to affect one of the following can elevate ICP: (1) addition of sufficient intracranial volume to overwhelm compensatory mechanisms, (2) impairment of the normal regulation of intracranial blood flow in the arterial, capillary, or venous phase, or (3) impairment of normal CSF production and absorption. A list of conditions known to potentially elevate ICP can be found in Table 1. The underlying pathophysiologies as represented here are highly oversimplified. Many of the disease states listed provoke all effects to some extent, in changing proportions over the natural history of the disease; this table is introductory, not encyclopedic.

FINAL COMMON PATHWAYS OF BRAIN DAMAGE

Clinical Presentation

The clinical manifestations of the conditions mentioned in Table 1 are variegate because symptoms are a function both of ICP generally and any focal areas of brain dysfunction because of the pathologic process. The essential clinical manifestations of raised ICP are the same, regardless of the cause: headache, nausea, vomiting, blurred vision, and somnolence progressing to coma. Idiopathic intracranial hypertension, cerebral venous thrombosis, obstructive hydrocephalus, and high altitude cerebral edema, for example, typically present in this fashion. Acute expanding masses that have minimal direct effect on cortex or white matter tracts, such as an epidural hematoma, may produce no focal deficit before elevating ICP dramatically, and will therefore present clinically with the above nonspecific symptoms. By contrast, highly destructive lesions such as a cerebral metastasis will often produce highly focal neurologic deficits long before they reach sufficient size to elevate ICP. Less destructive lesions, such as a subdural hematoma, may only produce more widely distributed localized signs (e.g., mild weakness with impaired sensation over the contralateral body) before producing the nonspecific symptoms of intracranial hypertension. Impairment of consciousness is a final common expression of more than one mechanism, because patient series have demonstrated that mental status correlates moderately at best to ICP *(47)* and to the degree of midline shift *(48)*, demonstrating that other mechanisms must have been operative in each case. Clinical presentation of rising ICP is thus any combination of the essential symptoms of elevated ICP, the localizing signs from any causative or concurrent mass, and the consequences of deformation of brain that are called the herniation syndromes.

Impaction: The Herniation Syndromes

Herniation refers to passage of an organ or part thereof past a boundary or into a space where that organ should not be. Mass effect in the brain not infrequently results in placement of pressure on structurally susceptible areas, producing specific constellations of symptoms and signs.

Uncal (Lateral Transtentorial)

Uncal herniation refers to herniation of the medial temporal lobe (uncus) past the edge of the tentorium and downward, impacting on cranial nerve III. Caused by swelling or mass effect in the temporal lobe or temporoparietal junction. When of sufficient magnitude, pushes the midbrain to the

Table 1
Predominant Pathophysiology of Selected Disease States

Disease state	Increased CSF volume	Increased blood volume	Mass effect	Increased intracellular brain water	Increased extracellular brain water
Trauma	+/–	+/–	+/–	X	X
Hypoxia/ischemia (diffuse) (postcardiac arrest, near drowning)		+/–		X	+/–
Ischemic stroke (focal)			+/– (late)	X(early)	X(late)
Subarachnoid hemorrhage	X				X
Intracranial hemorrage			X		X*
Subdural hematoma			X		
Epidural hematoma			X		
Obstructive hydrocephalus	X				X
Cerebral venous sinus thrombosis	X	X			X
Idiopathic intracranial hypertension	X				X
Normal perfusion pressure breakthrough (postoperative phase of AVM repair, A-V fistula repair, or CEA)		X			X
Tumor			X		X*
Abscess			X		X*
Empyema			X		X*
Meningitis	+/–	X			X
Encephalitis		+/–		X	X
Malignant hypertension and eclampsia		X			X
Fulminant hepatic failure/Reye's synd.		+/–		X	+/–
H_2O intoxication				X	
Lead intoxication				X	
High-altitude cerebral edema (HACE)				+/–(?)	X
Hypercarbia (COPD, Pickwickian synd., permissive hypercapnia)		X			
Tension pneumocephalus			X		

*Adjacent edema produces this effect.

X, present; +/–, may be present; AVM, arteriovenous malformation; A-V, arteriovenous; CEA, carotid endarterectomy; COPD, chronic obstructive pulmonary disease; CSF, cerebrospinal fluid.

opposite side, impacting the contralateral cerebral peduncle on the contralateral tentorial edge, with resulting pyramidal weakness; this "Kernohan's notch" phenomenon is a false lateralizing sign because the weakness is ipsilateral to the causative mass effect.

Tonsillar (Foraminal Impaction, Cerebellar Cone)

Tonsillar herniation refers to mass effect from above shifting the pontomedullary junction down through the foramen magnum. With impaction of the cerebellar tonsils therein, the medulla is compressed, resulting in dysregulation, then collapse, of respiratory and cardiovascular systems. This impaction also precludes further CSF flow out of the cranium into the spinal cisterns, with subsequent dissociation of intracranial CSF pressure (which often thence exhibits a profound further increase) from lumbar CSF pressure (which may return to normal).

Subfalcine (Cingulate, Supracallosal)

Subfalcine herniation refers to mass effect in the high lateral frontal or parietal lobe forcing the cingulate gyrus up against and then under and past the falx cerebri. This produces personality change and mild contralateral leg weakness, which becomes more pronounced if the herniation is of sufficient magnitude to compress the anterior cerebral artery (ACA) against the falx and cause an ACA infarct.

Central Transtentorial

Central transtentorial herniation refers to diffuse bilateral hemispheric swelling with progressive decline in mental status and decompensation of respiratory function, correlating somewhat with the degree of downward displacement of the midbrain through the tentorial hiatus. When of sufficient degree, the mesial temporal lobes impact in the tentorial incisura, creating a CSF block at that level. This results in the same compartmental CSF pressure dissociation effect as produced by tonsillar impaction, except with the dissociation arising between the supratentorial and infratentorial compartments.

Upward Transtentorial (Reversed Tentorial)

Upward transtentorial refers to mass effect in the posterior fossa displacing the midbrain upward. This may produce diffuse symptoms of obstructive hydrocephalus if the cerebral aqueduct or fourth ventricle is occluded, or homonymous hemianopsia if the posterior cerebral artery (PCA) impacts on the tentorial edge, or variegate neurologic deficits if the great vein of Galen impacts on the tentorium, producing infarcts in the deep venous territory (thalami, internal capsules and basal ganglia).

Transcalvarial (External)

Transcalvarial herniation refers to focal cortical signs because of herniation of cortex through a defect in the skull. Seen rarely, as patients with such defects are usually unconscious, as a result of diffuse injury if the defect is traumatic or general anesthesia if it is surgical.

Abducens Nerve Palsy

While its dysfunction is not classically considered a herniation syndrome per se, the structurally susceptible position of the cranial nerve VI is of note with regards to the symptoms of elevated ICP. With substantial displacement of the pontomedullary junction downward or to the side, one or both of the sixth cranial nerves can be stretched sufficiently to produce dysfunction of the nerve and failure of abduction of the ispilateral eye. Most commonly seen in association with central transtentorial herniation, it can be seen in isolation or with any of the other herniation syndromes.

Ischemia

Herniations produce focal tissue damage by impacting brain or vasculature against rigid structures. The other fundamental process by which intracranial swelling or mass effect can produce brain damage is by raising the intracranial pressure to the point that cerebral perfusion pressure, MAP-ICP, is compromised. If ICP encroaches on CPP, cerebral arteries will dilate in an effort to preserve blood

flow, CBV will increase, and ICP will further increase—the vicious spiral of mutually worsening ICP and ischemia. At its most pathologic extreme, this process proceeds until ICP equals MAP, CPP is abolished altogether, intracranial blood flow ceases, and the brain dies. Intermediate degrees of CPP impairment produce ischemic brain damage, resulting in neurologic deficits upon recovery. In an attempt to allow a safety margin above impending ischemia, CPP should be maintained at 70 mmHg if possible. This safety margin permits for the development of unappreciated pressure gradients within the brain, decreasing the chance that critically depressed CPP will develop at some point distant from the point at which ICP is being assessed. Attempting to maintain a target CPP, however, requires direct assessment of ICP-ICP monitoring, the means for which will now be discussed.

MONITORING THE PATIENT WITH POTENTIALLY ELEVATED INTRACRANIAL PRESSURE

The neurointensive care clinician must be attentive to all potential evidence of cerebral edema or intracranial hypertension. Currently, ICP can only be reliably assessed by invasive, neurosurgical means, which have relatively uncommon but potentially catastrophic complications. Many other noninvasive means of assessment must be used—to complement an invasive ICP monitor once one is in place, and during all phases of care when an ICP monitor is not in place. These will be discussed first.

Indirect Monitoring Techniques

Monitoring Clinical Status

The foremost noninvasive variable that must be followed, of course, is the clinical examination. The components of the neurological examination which we believe should be fully assessed and documented in the chart on at least a daily basis are presented in Table 2. Frequent and consistent documentation of these few variables permits dependable comparison between examiners of vital aspects of the patient's clinical status. Obviously, neither list even begins to approximate a complete neurologic examination; we wish to highlight here a select few items on the examination that are of high importance in assessing for a pathologic change in the nervous system, and can be done efficiently with a high degree of reproducibility between examiners. In patients with potential for elevated ICP, assessment of gag or cough and response to noxious stimuli may need to be omitted to avoid precipating plateau waves.

From the standpoint of assessing for the possibility of increased intracranial pressure, the paramount clinical findings to assess for are:

1. Level of alertness and GCS;
2. Pupillary examination;
3. Ocular motor examination (with special attention to the third and sixth cranial nerves);
4. Motor examination with special attention for hemiparesis;
5. Presence of nausea or vomiting;
6. Complaints of headache; and
7. Current vital signs and the recent course thereof.

Ophthalmoscopy, once of singularly central significance in the assessment for elevated intracranial pressure, has receded in importance in the era of modern neuroimaging. Papilledema does not develop until elevated ICP has been present for longer than 1 d. It should nonetheless be assessed for on initial evaluation, as its presence or absence (along with its sudden appearance in the context of previous absence) can provide useful information regarding the time course of the disease process.

Neuroimaging

Any patient in whom elevated ICP is suspected should at the very least receive an emergent noncontrast-enhanced head CT scan. Particular note should be made of any of the findings listed in Table 3, which suggest pathological states with the potential to cause intracranial hypertension. The

Table 2
Essential Components of the Clinical Examination in the Neurocritical Care Unit

In the conscious patient
Language, to include at least comprehension, repetition, fluency, and dysarthria
Ocular motor examination (eye movements), including any subjective diplopia or nystagmus
Visual fields, to finger-counting, in all quadrants (or blink to visual threat if unable to comply)
Pupillary examination
Facial symmetry
Motor examination including proximal and distal strength in all limbs, and presence or absence of pronator drift of the arms
In the patient with impaired consciousness
GCS
Pupillary examination
Visual pursuit (eye tracking) of the examiner or another visual target
Blink to visual threat
Oculocephalic reflex ("doll's eyes" maneuver), if C-spine is not immobilized
Gag or cough
Nature of response to noxious stimuli (as outlined on motor scale of GCS), documented separately for all 4 limbs, especially with regard to symmetry

presence of more than one of these abnormalities is highly suggestive of elevated ICP *(49)*; the presence of any one suggests the potential for it. MRI or contrast-enhanced CT can be pursued if necessary to better characterize intracranial pathology (*see* Chapter 7); for initial decision making, although noncontrast-enhanced CT is often sufficient.

The essential decision which must be made in patients with potentially elevated ICP is whether a monitoring device should be placed (*see* Direct ICP Monitoring section). Neuroimaging is used to establish diagnoses that produce the risk of elevated ICP, supplementing information derived from the history and examination. Imaging cannot substitute for invasive ICP monitoring. Repeat CT scans can, however, be used beneficially when the patient's clinical status is just short of requiring placement of an ICP monitor. In these circumstances, repeat imaging whenever the patient's status changes can document the appearance of a new finding (e.g., delayed hematoma in head injury) *(50)*, which can then prompt monitor placement. This approach can be utilized to delay or avoid monitor placement in cases where the need for it is initially equivocal.

Neurosonology

Transcranial Doppler ultrasonography (TCD) has been proven a useful clinical tool for noninvasive assessment of basal arterial cerebral blood flow, and is now available from most tertiary hospital vascular sonography laboratories *(51,52; see also* Chapter 6*)*. All of the major intracranial arterial branches can usually be insonated—middle, anterior, and posterior cranial arteries across the temporal bone (except in 10% of patients, in whom transtemporal insonation is impossible), ophthalmic artery and carotid siphon across the orbit, and vertebral and basilar across the foramen magnum from below. TCD reveals the velocity of blood flow, in centimeters per second, which typically ranges from 40 to 70. A second essential monitoring variable is derived from the waveform recording: the pulsatility index (PI), the ratio of the difference between systolic and diastolic flow to diastolic flow ([systolic flow – diastolic flow] / diastolic flow), typically approximately equal to 1.

Table 3
Neuroimaging Findings Suggestive of Deranged Intracranial Dynamics

Intracranial blood (epidural, subdural, subarachnoid, intraparenchymal, or intraventricular)
Obstructive hydrocephalus (dilated lateral ventricles or luncency of white matter near the anterior horns of the lateral ventricles consistent with transependymal flow)
Diffuse or focal cerebral edema (blurring of the interface between gray and white matter or effacement of sulci)
Midline shift (most readily discerned at the septum pellucidum, the pineal gland, and the fourth ventricle)
Compression of basal cisterns (especially the ambient and perimesencephalic)
Obliteration of the third ventricle

The most common clinical use of TCD is monitoring for vasospasm, especially after SAH. With narrowing of the arterial lumen, systolic flow increases and diastolic decreases (systolic flow of 120 is highly suggestive and 200 confirmatory of decreased luminal diameter), resulting in an increase in PI (values above 3 : 1 are highly suggestive of luminal narrowing) *(53)*. Frequent serial TCD assessments can detect the progressive changes in flow velocity and PI which SAH vasospasm produces *(54)*.

Luminal narrowing can be produced by intrinsic constriction of arteries themselves—by smooth muscle action, as in autoregulation and true vasospasm, or by intimal hyperplasia as in the "vasospasm" of SAH. Vasospasm can also, however, by produced by extrinsic compression of arteries—most notably, diffuse elevation of ICP produces a compressive force that causes the basal arteries to be narrowed. Generalized increases in flow velocity and PI can therefore indicate diffuse extrinsic compression of arteries owing to increased ICP *(55)*. Unfortunately, despite the ability to demonstrate such changes, TCD is insufficiently sensitive and specific to provide a noninvasive alternative to ICP monitoring. It cannot substitute for direct ICP monitoring. The clinician who is using TCD to monitor SAH patients for arterial narrowing should thus bear in mind that diffusely distributed changes indicative of luminal narrowing may indicate increasing ICP.

Some attempts have been made to utilize TCD to assess for loss of autoregulation and for the presence of a critical MAP below which CPP is compromised *(56)*. Unfortunately, these uses have proven too insensitive and cumbersome to gain widespread acceptance.

Direct ICP Monitoring

At present, no means of accurately assessing ICP has yet been developed that does not require surgical placement of an invasive device. All such devices have attendant risks, mostly of hemorrhagic and infectious complications (discussed below; *see also* Chapter 6). The decision as to when an ICP monitoring device should be placed is therefore delicate, as equipoise must be achieved between the benefits to be derived from knowing the ICP versus the potential for morbidity and mortality attendant on device placement. Data regarding complication rates are of middling quality at best. Although there is no question that in some circumstances ICP monitoring provides treatment-altering and life-saving information, it is a sad fact that no systematic data are available for any clinical condition to help guide clinicians in judging when the benefits of monitor placement outweigh the risks.

Decision making with regard to which patients stand to benefit from ICP monitor placement can be difficult indeed. Generally, a device should be placed if (1) the condition leading to ICP elevation is amenable to treatment, (2) ongoing direct assessment of ICP will be of consequence in decisions regarding treatment interventions, and (3) the risks of device placement do not outweigh the potential benefits. If ventricular CSF drainage will be of instrumental use in decreasing ICP, then (4) a device with the capacity to drain CSF should be placed, again provided that the risks are not prohibitive. Most recent reviews *(10,14,47,56)* agree that the threshold for ICP monitor placement in the moderately to severely head injured patient is a GCS of 7–8 or less, or the presence of sufficient injury to other organ systems that either (a) aggressive treatment for hypotension or (b) endotracheal intubation are necessary *(10,14)*. There is general agreement that in the patient with subarachnoid hemor-

rhage, the development of hydrocephalus should prompt intraventricular catheter placement *(57,58)*. Few reviews offer good guidance regarding ICP monitor placement for any other condition listed in Table 1. In general, recommendations are offered by some that patients with a disease that is amenable to treatment have a monitor placed if the GCS is 7–8 or less *(10,57)*. In the end, the clinician must attempt to weigh considerations (a–d) for each patient. It is likely that with the further evolution of neurologic critical care, collective experience will permit the development of guidelines for other conditions.

Intraventricular Catheter (IVC)

The gold standard device for monitoring of ICP is a hollow catheter inserted through a burr hole, across the meninges and the brain, and into the cerebral ventricle *(14,56)*. A pressure transducer at the extracranial end of the device measures the pressure exerted through the catheter by the CSF. Because fluids convey pressure well, the CSF pressure thus measured can be regarded as representing the average pressure of the intracranial contents. The inherent accuracy of this arrangement makes the intraventricular catheter the "gold standard" of ICP monitoring devices. Its other chief advantage is the capability to drain CSF. As will be discussed, CSF drainage can be a potent means of decreasing ICP. However, there are several disadvantages to the IVC. If the lateral ventricle is collapsed, it cannot be placed. At 1–6%, it has the highest risk of hemorrhage of any of the devices; hemorrhage typically occurs at the time of insertion but can be delayed, and it can occur in subdural, intraparenchymal or ventricular spaces *(56)*. Lastly, infection can occur in any of the spaces through which the catheter passes—skin wound infection, calvarial osteomyelitis, subdural empyema, meningitis, parenchymal abscess, or ventriculitis *(56)*. Infection rates of 2–22% have been reported for intraventricular catheters *(59–61)*. The available literature is equivocal with regards to whether the prophylactic use of antibiotics–in usual clinical practice an antistaphylococcal penicillin (e.g., nafcillin)—consistently reduces the chances of infection *(60–62)*. Prophylactic antibiotics nonetheless remain standard practice for many clinicians. Most patient series consistently show few infections earlier than 3 d after catheter insertion, with most occurring after 5 d or later *(59, 60, 63)*. This led to the recommendation that any catheter required for longer than 5 d be replaced *(56,60)*. More recent data, however, do not indicate any decrease in the infection rate resulting from such "prophylactic" catheter exchange *(64)*, and also appear to show that while infection rates continue to rise from d 5 through d 10, infection after d 10 is rare. The most prudent course of action therefore is to maintain scrupulously sterile technique with intraventricular catheters, and to remove them as soon as possible, with no exchanges of new catheters for old. Flushing of catheters increases the risk of infection, and should be avoided *(60,61)*.

Parenchymal Catheters

The commercially available Camino catheter, also inserted through a burr hole and then the meninges, can be passed into either brain parenchyma or the lateral ventricle *(65)*. A fiberoptic transducer measures the pressure at the tip of the catheter. A similar parenchymally placed catheter with a strain-gauge transducer in the tip is also available *(66)*. The chief disadvantage of these devices is the inability to withdraw CSF. Other disadvantages are a tendency for pressure readings to "drift" over time; susceptibility to pressure gradients across brain tissue, when inserted into parenchyma; and risks of hemorrhage and infection similar to those of the IVC, with the exception that when passed only into parenchyma there is no risk of ventricular hemorrhage or ventriculitis. The chief potential advantage of these devices over the other non-IVC devices is a higher degree of accuracy of pressure measurements, but there are not enough data to substantiate this.

Subarachnoid Bolt

This device consists of a hollow saline-filled bolt which is screwed into a burr hole until its leading edges are flush to the dura *(67,68)*. With an incision in the dura at the opening of the lumen, the saline

in the lumen is continuous with the CSF in the subarachnoid space; the fluid pressure in the bolt lumen is then taken to be equal to ICP. The chief advantages of this device are ease of insertion, much lower rates of hemorrhagic complication, and infectious complications in the range of only 2–7% *(59,61,69)*. Along with the inability to withdraw CSF, and questionable accuracy, an important limitation of this device in conditions of increased ICP is the possibility for swollen brain to herniate through the calvarial defect and occlude the lumen of the device. There is also a greater propensity to device occlusion than with intraventricular catheters *(70)*, necessitating device flushing, which increases the risk of infection *(61)*. Although this can be avoided by leaving the dura intact and thus assessing epidural and not subarachnoid pressure, this modification further decreases the accuracy of the device.

Epidural Device

Fiberoptic- and the strain-gauge–tipped catheters can also be placed into a pocket between the dura and the calvarium *(65,66)*. The chief advantage of such placement is a very low rate of hemorrhage and infection *(65,66)*; this comes at the cost of further tendency toward inaccuracy, and once again does not permit CSF drainage *(14)*.

Clinical Use of ICP Monitors

The simplest and most common use of ICP monitor data is assessment of the ICP itself, with titration of treatment to the concurrently measured pressure. Ideally, however, it would be preferable to anticipate ICP elevations before they happen, so that measures can be taken to prevent them. At any given time, the clinician would therefore prefer to know not only the instantaneous value of ICP, but also whether the intracranial system is in a state of normal or altered compliance (i.e., one would like to know not only the ICP, but the slope of the pressure-volume curve at that time).

The most straightforward means to assess concurrent intracranial compliance is visual examination of the ICP waveform, as discussed in Fig. 3. Merging of the P1 and P2 waves is highly suggestive of decreased compliance, and the potential for increases in ICP. Currently, visual inspection of waveforms may be the most widely utilized means of compliance assessment.

Efforts have been made at direct assessment of compliance. Miller and colleagues *(71–74)* demonstrated that the response of ICP to injection or withdrawal of a set amount of fluid through an intraventricular catheter could be used to assess compliance, and termed this change the volume-pressure response (VPR). In this paradigm, the greater the pressure change in response to a set change in volume, the lesser the intracranial compliance. This means of assessment has been standardized by means of the pressure-volume index (PVI), which is calculated as:

$$PVI_i = V_i / \log(P_p/P_o)$$

where: V_i = injected volume;
P_p = peak ICP after injection; and
P_o = initial ICP before injection *(56)*.

PVI_w can also be defined as the equivalent value when a volume of fluid is withdrawn to derive it, and tends to be a lower and hence less accurate assessment of the true value *(56)*. Based as it is on logarithmic values, the PVI expresses the volume that must be injected into (or withdrawn from) the system in order to change the ICP by one log (a factor of 10), and hence it is not intuitively appealing. However, it does permit standardization for different values of injected or withdrawn fluid, and it permits establishment of normal ranges—PVI values greater than 20 mL indicate normal compliance, between 20 and 15 mL decreasing compliance, and less than 15 mL significantly decreased compliance. The PVI itself has subsequently been modified into a direct expression of compliance: $\mathbf{C = 0.4343(PVI/P_o)}$ *(75)*. For various reasons, however, these means to assess compliance have not become standard practice—the degree of accuracy and reproducibility is disappointingly low, and the necessary manipulation of CSF through the intraventricular catheter increases risk of infection and entails a risk of precipitation of plateau waves *(56,60,61)*. One modification involves the use of

extremely small volumes (0.5 mL), with a square-wave injection-withdrawal method, the short pulse response (SPR) *(76)*; another involves the use of a double-lumen device with similarly small volumes of injection *(77)*. Although no such direct assessment has yet been proven both reproducible and safe, there is no doubt that such a clinical tool would be highly useful; it is to be hoped that continued research in this area will bear fruit.

CBF MONITORING: BRIEF OVERVIEW

As discussed previously, the predominant final common pathway of brain injury in states of altered intracranial dynamics is ischemia. The ideal parameter to monitor to prevent such damage, then, would be regional CBF. A variety of means are available for such assessment *(78)*. Each available means of assessment, however, has significant limitations. The only currently available technique that provides information about the adequacy of specific regional blood flow is PET scanning, which is only available at a few academic centers. As discussed previously, TCD can be used to follow the velocity of blood flow in the basal intracranial arteries; the other commonly used techniques, Xenon clearance/Xenon CT and jugular venous oxygen saturation ($SjvO_2$) monitoring, are discussed in Chapters 3 and 6, respectively.

INTERVENTIONS

This section will review the various therapeutic interventions at the clinician's disposal in treating the patient with potential or realized cerebral edema and/or intracranial hypertension. Two fundamental questions must be kept in mind at every phase of care of a patient with potential brain edema or elevated ICP—whether an invasive ICP monitor is necessary and if the patient should be taken to the operating room for craniotomy. Surgical treatments will therefore be discussed first in this chapter. They are on occasion definitive, dramatically decreasing the need for further medical interventions; there are many circumstances in which no amount of medical management will achieve normalization of ICP while a space-occupying mass remains in place; and a consideration of surgical treatment can be much briefer than a discussion of the many medical measures available to the clinician. Lest this secondary placement of medical treatment be misconstrued, it must be reinforced that in most patients who have a lesion excised to control ICP, the principles of general medical management outlined here must be scrupulously followed in the perioperative and postoperative period if the full benefits of surgery are to be realized.

Surgical Interventions

Resection of Source of Mass Effect

If ICP is elevated because of a space-occupying lesion, no amount of medical intervention will satisfactorily normalize it; intracranial masses producing elevated ICP must be resected. Epidural hematoma, with bleeding into the epidural space under arterial pressure, has the potential to compromise CPP profoundly and precipitously, and evacuation is a hyperacute surgical emergency *(79)*. Acute subdural hematoma collects less rapidly and under less pressure, but what data are available are highly suggestive that surgical evacuation within 4 h improves outcome *(80)*. Brain abscess must be drained or resected to relieve mass effect *(81–84)*. Pneumocephalus must be evacuated if it is under sufficient tension to increase ICP. Spontaneous intracerebral hemorrhage is controversial; while most surgeons will elect for surgical drainage, it is far from clear from the available literature that this approach improves outcomes *(85,86; see* Chapter 19 for further discussion). Decision making regarding brain tumors is complex, taking into account the number and location of space-occupying lesions, and the expected response of the tumor type to chemotherapy and radiation; for reasons of space, this issue will not be discussed further.

CSF Drainage

It has been known for some time that extrinsic drainage of CSF can be a highly potent means to control elevated ICP. As discussed previously, an increase in the resistance to resorption of CSF (R_o) is probably, to a greater or lesser degree, part of the pathophysiology in most conditions that increase ICP *(45,46)*. Direct CSF drainage in effect decreases R_o.

Intraventricular CSF Drainage

In standard clinical practice, CSF drainage has generally been accomplished via intraventricular catheter. This approach permits the conceptually and technically straightforward approach of draining CSF at any set pressure "above head level"—i.e., the threshold of CSF drainage is set manometrically (usually 20–25 cm CSF above the approximate level of the foramen of Monro), such that so long as catheter pressure exceeds this threshold and the system remains patent, CSF continues to drain. An intraventicular catheter is also the only appropriate intervention if obstructive hydrocephalus is present. As discussed previously, however, intraventricular catheters have a higher complication rate than other available ICP monitoring devices. Moreover, in some cases of ICP elevation, particularly those owing to head trauma, collapse of the ventricle due to parenchymal swelling may render catheter placement impossible.

Lumbar CSF Drainage

Several recent publications have drawn attention to an alternate means of CSF drainage, the lumbar drain *(87–89)*. Commonly utilized to produce a below-normal CSF pressure in order to decrease the incidence of CSF fistulae in cranial base surgeries *(90,91)*, these reports have focused instead on normalizing elevated CSF pressure. From the conceptual standpoint of decreasing R_o, the location from which CSF is drained matters little, and lumbar cistern catheter placement does not carry with it the same intracranial hemorrhagic risks as does intracranial catheter placement.

The most obvious potential adverse result of draining CSF from the spinal cistern is the precipitation of foraminal impaction of the cerebellar tonsils, uncal herniation over the tentorium, or the induction of severe spinal cord compression at an area of spondylotic narrowing with previously mild compression ("spinal coning"). While the total number of patients in these reports is low, such an effect did not occur in any of the reports, which drew on a population of head-injured and post-SAH patients *(87–89)*. The authors universally minimized the chances of such an event by using drainage only for patients in whom the basal cisterns were present and open on head CT. No cases of herniation were reported in the two reported series of patients treated with continuous lumbar CSF drainage *(91,92)*; however, of the 91 total patients so treated, a minority had conditions potentially consistent with elevation of ICP, and no ICP data are reported. Noteworthy complications in these reports include two cases of reversible vocal cord paralysis attributed to vagus nerve rootlet traction, a PCA distribution stroke attributed to PCA impaction on the tentorial edge, and a partial cauda equina syndrome with urinary retention that resolved after CSF catheter removal. It is also noteworthy that collectively, these series report 12 cases of meningitis complicating lumbar drains; in both series, prophylactic antibiotics were not utilized. Two patients died: aspiration pneumonia developed in 1 patient with vocal cord paralysis, and hepatic failure developed in 1 patient with meningitis. Minor complications were quite common: headache (26/91) and radicular pain (7/91), in particular. Lumbar CSF drainage would therefore appear to be fairly safe, in these series; however, few of the patients reported likely had elevated ICP, and two deaths did occur. To our knowledge, there is only one series available reporting simultaneous intraventricular and lumbar CSF pressures, recorded both before and after lumbar CSF drainage in patients with subarachnoid hemorrhage (SAH) *(93)*. These authors found that in 13 of 14 patients so evaluated, ventricular and lumbar CSF pressures were nearly equal both before and after lumbar CSF withdrawal. In the fourteenth patient, however, ventricular pressure after lumbar withdrawal was unchanged vs before, despite lumbar pressure having decreased by

19 cm H_2O. This report sounds a note of caution—when utilizing lumbar CSF drainage, careful attention should be paid that intracranial pressure is comparable to lumbar pressure or appropriately responsive to drainage from the lumbar cistern. Whether because of intracranial herniation at the tentorial hiatus or foramen magnum, spondyloarthropathic compression of the thecal sac in the spinal canal, or inflammatory obstruction of the subarachnoid space, subarachnoid block does occur, and its presence must be ruled out if lumbar CSF drainage is to be utilized safely and effectively.

Other reports of this approach to patients with ICP elevation are few. Two patient series do report the use of lumbar CSF drainage for cryptococcal meningitis with signs of ICP elevation *(94,95)*, and found the technique safe and effective. A cautionary note was sounded by another report of SAH patients, in which continuous CSF drainage was associated with an increased incidence of delayed ischemic deficits and shunt-dependent hydrocephalus. The technique in this series involved deliberate induction of CSF hypotension by overdrainage of CSF, and it thus seems likely that drainage to maintain CSF normotension should not be considered contraindicated for SAH patients on the basis of this report; induction of hypotension, in contrast, should be carefully avoided. Regarding to the laboratory evaluation of CSF so obtained, it has recently been demonstrated that CSF obtained from the lumbar space yields nearly the same erythrocyte and leukocyte count and differential when compared to simultaneous samples from the intraventricular space; glucose is only one-fifth lower in the lumbar than in the ventricular CSF *(96)*. Lumbar CSF can thus be regarded as interchangeable with ventricular CSF when assessing for meningitis.

At this time, pending publication of a sizable series of patients so treated, lumbar CSF drainage remains an attractive alternative whose relative risks and benefits remain ill-characterized. However, it is worth noting that the very same criticism can be justly made of ventricular catheters. A cautious approach to its use is appropriate, given the catastrophic consequences should herniation be induced. Spinal block should be carefully evaluated for and ruled out, and drainage should be titrated if possible to directly measured ICP, to avoid overdrainage and the induction of CSF hypotension. Provided these precautions are kept in mind, lumbar CSF drainage can be a useful tool in control of ICP.

Craniectomy

Possibly the most radical intervention for intracranial hypertension, the surgical removal of part of the calvarium creates a window in the cranial vault, negating the Monro-Kellie doctrine of fixed intracranial volume and allowing for herniation of swollen brain through the window to relieve pressure. Although described at least as early as the first decade of the twentieth century *(97)*, consistently poor outcomes led to its being regarded as a futile exercise *(98)*. A large number of reports since 1990 have revisited this issue, studying its use for treatment-refractory intracranial hypertension in head injury *(99–105)* and for large, space-occupying hemispheric stroke *(106–109)*. The approach in these trials has been the removal of a calvarial bone flap extending from above the orbit anteriorly to a few centimeters from the occipital pole posteriorly, and from near the midline medially to the vicinity of the floor of the middle cranial fossa near the origin of the zygoma laterally, thus creating a very large fenestration. The head-injury series have reported outcomes similar to or slightly better than historical norms, and outcomes in the stroke series appear similarly optimistic. To date, however, no trial has yet been reported for either condition which has randomized similar patients to either receive surgery or not. It is therefore impossible to know with certainty that this risky and highly expensive measure actually improves outcomes. Until such publication, it could be argued that hemicraniectomy should remain an experimental procedure; in some centers, however, sufficient experience has accrued that hemicraniectomy is beginning to become standard practice. Unfortunately for those patients and physicians not in these centers, insufficient formal evaluation of this technique has yet been published to offer good guidelines for its use.

Medical Interventions

General Cardiopulmonary and Metabolic Support

There are several principles of general patient care that should be scrupulously applied in all cases of manifest or impending intracranial hypertension. These measures are undertaken with the intent to avoid precipitating or exacerbating increased ICP, and should be followed fastidiously; in any patient with decompensated ICP requiring acute intervention, it is also worthwhile reviewing to these general principles of medical support to ensure that none have been overlooked. These guidelines are largely based on an understanding of the pathophysiology of deranged intracranial dynamics as discussed previously, but many are supported by patient data as well.

Hemodynamics

Understanding of cerebral autoregulation dictates a few general guidelines that should be followed with regard to volume status and blood pressure management. In any patient with deranged intracranial dynamics, systemic hypotension must be avoided if at all possible. In a patient with elevated ICP and intact autoregulation, the vasodilatory response to decreased MAP will increase CBV and possibly precipitate a plateau wave *(42)*. In a patient with regional or global failure of autoregulation, hypotension will produce decreased CBF and ischemia. Some *(39,56)* have recommended pharmacologic elevation of MAP in all patients with elevated ICP, reasoning that elevated MAP will provoke vasoconstriction, decreased CBV, and a resulting drop in ICP. There is one head injury trial that appears to lend some support to such an approach *(110)*. There is a theoretical risk, however, that elevating intravascular pressure will exacerbate edema formation if the BBB is ruptured. It seems prudent, therefore, to use pharmacologic elevation of MAP only if an ICP monitor demonstrates a favorable response to a trial of a vasopressor.

Hypertension should only be pharmacologically lowered if there is reasonable clinical suspicion that it is directly responsible for deleterious consequences (hypertensive encephalopathy, retinal damage or renal damage), and then only if the lowering does not produce cerebral ischemia. Whenever possible, the vasodilating agents (nitroglycerin, nitroprusside and hydralazine) should be avoided because they directly dilate cerebral vasculature, potentially exacerbating cerebral hyperemia; labetolol is typically considered the agent of first choice for lowering blood pressure *(39)*.

Maintenance of normal to slightly elevated blood pressure dictates maintenance of normal to slightly expanded intravascular volume. This should be accomplished with isotonic fluids only, preferably 0.9% normal saline. Hypotonic fluids should be strictly avoided because the free water fraction of any such fluid is free to pass out of the intravascular space into the brain and thus contribute to cerebral edema. The only exception to this rule is the case of reversal of hypernatremia, which should be undertaken only when cerebral edema and intracranial hypertension are sufficiently controlled to permit it, and then in a slow gradual fashion with a few hundred milliliters of free water in each day's total fluids.

These are the general principles of fluid management that should be applied to all patients with or at risk of increased ICP. The deliberate use of hypertonic solutions is a separate matter, discussed in the Hypertonic Saline section.

Glucose

In ischemic stroke patients, hyperglycemia has been associated with a three times greater likelihood of poor outcome (regardless of whether the patient was previously diabetic or not) *(111–113)*, is correlated with larger stroke size *(114)*, and is an independent predictor of intracranial hemorrhage complicating intra-arterial thrombolysis *(115)*. It is an independent predictor of poor outcome in subarachnoid hemorrhage *(116)*, and meningitis *(117)*. Hyperglycemia is also correlated with worse

outcomes in head-injured patients *(118–120)*. Investigation in intracranial hemorrhage has yielded conflicting results *(110,121)*.

These observational data have been taken as evidence that control of hyperglycemia is advisable in cerebrovascular patients particularly in the neurocritically ill. Data to support an improvement in outcome with an aggressive treatment approach to control serum glucose, however, are weak. A recent trial has reported significantly improved outcome in unselected intensive care patients who received an insulin drip titrated to maintain euglycemia *(122)*. Unfortunately, whereas 20% of the patient sample consisted of neurologically ill patients (mostly head injury and postcraniotomy), results were not independently reported for this subset. We are unaware of any similar trial of aggressive control of serum glucose in the neurocritically ill. Although it is reasonable to surmise that controlling serum glucose is highly likely to improve outcomes, this cannot be considered proven, and it is unclear what treatment approach (insulin drip, scheduled insulin, oral hypoglycemics, and so on) offers the best risk-benefit ratio. If an aggressive treatment approach is pursued, the clinician must take special care not to induce hypoglycemia, which could be disastrous to an already diseased brain.

Temperature

Fever is an expected feature of infectious conditions of the central nervous system (CNS). In other etiologies of deranged intracranial dynamics, systemic responses to infection or inflammation elsewhere in the body can have a significantly deleterious effect on the intracranial process. Patient data indicate larger stroke size and a worse outcome with fever in patients with ischemic stroke *(123,124)*, and worse outcomes in SAH *(125)*, diffuse anoxic injury *(126)*, and intracerebral hemorrhage *(121)*.

With fever as with hyperglycemia, these observational data, coupled with animal model data *(127,128)*, have been interpreted as supporting an imperative to treat. Far and away, the most frequently utilized means in the United States is acetaminophen; typical usage is 325–650 mg by mouth or rectum q4h as needed for fever. The high degree of safety of acetaminophen in routine clinical use would likely render unethical any placebo-controlled trial to demonstrate an improved outcome with its use for fever. Unfortunately, little study has yet been given to what constitutes optimal use of this agent, and whether other approaches would produce better outcomes. A single pilot study in patients with acute stroke has shown that patients randomized to 1 g of acetaminophen scheduled four times daily enterically or rectally had a substantially lower risk of developing fever over the ensuing 5 d than did patients given placebo *(129)*. In those who remain febrile despite acetaminophen, a small number may respond to an air-circulating cooling blanket *(130)*. Currently, further measures in such patients, whether other antipyretic agents might be of greater efficacy, and whether any approach to antipyresis actually produces improved patient outcome are all subjects still in need of clarification.

The therapeutic use of induced hypothermia is another matter entirely, and shall be discussed in the section that follows.

Nutrition

Prompt institution and maintenance of nutritional support is obligatory in patients with critical neurological illnesses; this is amply covered in Chapter 14 and is not further discussed here. However, it must be reiterated that special care should be taken to ensure that the osmotic content of all nutritional fluids should be such that there is no net administration of free water between enteral feedings, parenteral feedings and other intravenous fluids.

Ventilatory Support

Many patients with serious intracranial diseases require intubation (*see also* Chapter 9). Any patient with a GCS score less than 8 should be intubated for airway protection, as should any patient requiring general anesthesia for control of ICP. Intubation should also be pursued in any patient with intercurrent pulmonary disease—(e.g., acute respiratory distress syndrome (ARDS) or pulmonary

contusion acquired concurrently with head trauma, pneumococcal pneumonia intercurrent with meningitis, aspiration pneumonia subsequent to depressed level of consciousness or impaired pharyngeal control, etc.). Given the potential for hypercarbia and hypoxia to precipitate intracranial hypertension in patients with decreased compliance (or exacerbate it when already established), any patient at risk for elevated ICP should be intubated expectantly when the development of respiratory distress is anticipated.

Optimal ventilatory management in these patients has not been evaluated prospectively. However, on the basis of physiologic understanding and a few key observations that have been reported fairly consistently by multiple observers, a few guidelines can be offered.

The chief concern regarding to endotracheally delivered positive-pressure ventilation is the potential for elevation of central venous pressure with resulting inhibition of cerebral venous drainage, thus increasing ICP. After an initial report of just such a result in severely head-injured patients receiving positive end-expiratory pressure (PEEP) more than 10 cm H_2O *(19)*, subsequent reports in both head-injured *(131)* and SAH patients *(132)* have verified a slight increase in ICP with PEEP greater than 5 but have shown no clinical deterioration or other apparent deleterious consequences from this effect. Both of these studies documented an increase in MAP paralleling ICP, thus maintaining CPP greater than 60. It is therefore likely safe to use PEEP of up to 10 cm H_2O routinely when necessary to optimize oxygenation, and it may be safe up to 15 cm H_2O with careful direct observation to verify no adverse consequences. The guidelines offered are based on results reported from a total of 78 patients, all but 9 of whom had head trauma as the underlying disease process. In any individual patient, therefore, the effect of PEEP on ICP and CPP should be titrated on the basis of direct observation via pressure monitor, if possible.

Another source of concern in ventilated patients is the potential for coughing (spontaneous or induced by endotracheal suctioning) to produce spikes in ICP. Presuctioning endobronchial lidocaine *(56)* or increased sedation may be effective if such surges in ICP are encountered. If these measures prove ineffective, pharmacologic paralysis is an option *(39)*. These suggestions are entirely untested and empiric.

The deliberate use of hyperventilation as a specific therapeutic modality is discussed in the section that follows.

Patient Positioning

Elevation of the head, by decreasing CSF hydrostatic pressure and facilitating venous blood drainage, decreases ICP in normal humans *(17)* and in patients with head injury *(113)*. The robustness of the finding has led most practitioners to generalize its use, and recommend that patients with decreased intracranial compliance be positioned with the head elevated 30 degrees *(39,47,56)*. There is a single report of a few patients in whom such positioning actually increased ICP *(134)*. In this report, however, there were no patients whose ICP was observed to increase from below 20 cm H_2O supine to above 20 cm H_2O at an inclination of 60 degrees (that used by the authors). It is therefore likely safe to recommend the following approach: patients with some degree of suspected impairment of intracranial compliance but with insufficient indications for placement of an ICP monitoring device should be positioned at 30 degrees head elevation empirically; in patients with a monitoring device in place, the response of ICP to head elevation can be directly observed, and those few who have a higher ICP with head up can be positioned wherever ICP is the lowest.

Also of importance is that if at all possible no constricting garments or devices should encircle the neck (endotracheal tube tape, for example), as such items have the potential to compress the internal jugular veins and retard cerebral venous drainage. By the same token, the patient should be positioned with the head facing straight forward, as the head when turned to one side with the neck flexed can compress the internal jugular vein on that side. Although not prospectively evaluated, these measures are easily undertaken and we have seen them produce significant effects on ICP in a few patients.

Anticonvulsants

The systemic hypoxia, hemodynamic alterations and cerebral autoregulatory derangements that accompany seizures can produce real harm in some patients with increased ICP. Many practitioners therefore use prophylactic phenytoin therapy, particularly in patients with head trauma *(135)*, SAH *(136)*, intracranial hemorrhage *(85)*, and other conditions. Data are available to validate prophylactic anticonvulsant therapy only in the case of traumatic brain injury, for the first 2 wk after injury only *(135)*; when such prophylaxis should be discontinued in the head-injured is a matter of great controversy *(137)*. Prophylactic use of phenytoin in patients with brain tumors does produce a decreased risk of seizures, but at an unacceptable cost in adverse effects *(138)*. There are no good data to support the prophylactic use of anticonvulsants for any other condition. Current clinical practice in many centers is to use anticonvulsants prophylactically regardless of the lack of supporting data.

Antibiotics

Empiric antibiotics are frequently used in trauma patients when there is an appreciable clinical risk of wound infections from the initial injury. Their use for patients with intracranial ICP monitoring devices is discussed in the Direct ICP Monitoring section.

Specific Interventions

In patients with elevations of ICP sufficient to produce or threaten ischemia or herniation, there are a limited number of medical interventions which can sufficiently reduce intracranial volume to lower ICP and prevent or ameliorate tissue damage. Their proper use depends on the clinical context and an understanding of the time frame over which they have their effect and how large that effect can be.

Hyperventilation

As discussed previously, decreased carbon dioxide tension is a potent constricting stimulus to cerebral arteries. Decrease in CO_2 tension by 10 mmHg can produce sufficient reduction in CBV to effect a profound decrease in ICP. Unfortunately, this effect has several limitations. It may produce sufficient decrease in CBF to induce ischemia *(139)*. The constrictive effect on cerebral arterioles lasts a matter of 10–20 h, over which time cerebral arterioles redilate, possibly to a larger caliber than at baseline *(140)*; the initial reduction in CBV from hyperventilation thus comes at the cost of a possible rebound phase with *increased* ICP. Maintenance of deliberate respiratory alkalosis for a sustained time has been convincingly shown to worsen outcome in head injury patients *(141)*; even repeated serial episodes of hyperventilation may have deleterious consequences *(110)*. Although these results have not been replicated in other disease states, recognition of the temporary efficacy of this measure and its demonstrated potential adverse effects suggest that its use be limited to emergent situations in which there is an expectation of more definitive treatment to supercede in the near future. That is, hyperventilation is likely best used as a short-term measure, as a "bridge" to more definitive therapy *(142,143)*, never as a sustained therapy to be maintained for longer than a few hours at most. The best example of this use would be in a patient with an intracranial mass (hematoma, abscess) and signs of herniation, with use of hyperventilation during the time from recognition of the emergency to surgical evacuation of the mass; another example would be hyperventilation at the onset of a plateau wave while mannitol and barbiturates are being obtained and then administered. This approach, however, is not universal; despite the adverse outcomes demonstrated by Muizelaar and associates *(141)* with sustained hyperventilation, many practitioners still use it, even in head injury patients *(144,145)*. We recommend strongly against it.

Most authors agree that when hyperventilation is instituted, the goal should be lowering the pCO_2 by 10 mmHg, to approx 30 mmHg *(39,56,146)*. The best means by which to accomplish this is not known. Bingaman and Frank suggest tidal volumes of 12–15 cc/kg with a rate of 12–14/min *(47)*; Marshall and Mayer suggest rates of 16–20/min without specifying tidal volume *(146)*. All agree that

hypocarbia once induced should be reversed slowly, with recommendations ranging from 6–24 h *(39,47,146)*, to minimize the rebound hyperemia of re-equilibration.

Osmotherapy and Diuretics

Mannitol. Mannitol is the most widely used of a class of compounds intended to act as osmotic diuretics. The mechanism of action of the class is to increase serum osmolarity with a compound that has a high coefficient of reflection at the BBB, producing an osmotic gradient from the interstitial to the intravascular compartment, and thus pulling water out of the tissue. There is little doubt that brain dehydration, mainly from normal brain, is the predominant effect by which mannitol lowers ICP *(147,148)*. In the kidney, mannitol is filtered by the nephron, but unabsorbed by renal tubules; it then acts as an osmole in the lumen of the collecting duct, preventing resorption of water, producing a diuresis, and passing unmetabolized out of the body. Mannitol can therefore be conceptualized as a direct conveyer of free water from the diseased or injured brain through the kidneys and out of the body.

Mannitol has other mechanisms of action, however. It appears that mannitol reduces blood viscosity, perhaps by rendering erythrocyte membranes more flexible *(149)*. It appears that this produces a transient increase in cerebral blood flow and cerebral blood volume, and a compensatory vasoconstriction with a net reduction in CBV *(150,151)*. Mannitol may also decrease the rate of CSF formation *(148)*. By multiple mechanisms, then, mannitol removes volume from the intracranial compartment, lowering ICP.

Mannitol is generally utilized in boluses of 0.5–1.5 g/kg to lower elevated ICP, or when ICP elevation is suspected, but emergent evaluations (e.g., head CT) are yet pending. Several precautions should be taken in its administration. A urinary catheter must be in place to prevent bladder distention. Rapid administration of a bolus can produce immediate hypotension *(152)*, so isotonic fluid and a vasopressor agent should be immediately at hand *(39)*. A robust diuretic response can produce intravascular hypovolemia with resulting hypotension and even renal failure. Unless the patient is hypervolemic and a diuresis is desired, isotonic volume replacement should be maintained on an ongoing basis. Mannitol depletes body potassium, magnesium, and phosphorus *(153)*, rapid diuresis can produce an acute hyperkalemia *(10)*, and long-term use can produce sufficient derangement of renal medullary concentration gradients that nephrogenic diabetes insipidus results *(21,56)*. ICP typically responds briskly to mannitol administration, but may rebound again in a few patients, typically after 30–120 min *(154)*, requiring a repeat dose or some other intervention. Lastly, mannitol will pass out of the intravascular compartment and into the interstitium in areas of BBB damage, and thus may have the capacity to exacerbate vasogenic edema if used over a sustained time *(155)*. The demonstration of this phenomenon in an animal model *(155)* has led many to recommend that mannitol be used only in periodic boluses, not in frequent small doses to maintain a constant hyperosmolar state *(156)*. However, the model in question has a possible methodological confound (a net positive fluid balance in the animals given multiple boluses), and this potential adverse effect has not been convincingly demonstrated in human patients. Many practitioners therefore still use repeated doses of mannitol to maintain a "steady state" serum osmolality of 300–310 mOsm when a sustained effect of brain dehydration is desired. Whether this approach achieves its desired ends cannot be answered with certainty.

Which disease states mannitol is likely to treat with the greatest efficacy is not an issue which is well-established in the literature. Prospective evaluations of the use of mannitol in specific disease states are almost nonexistent. Conceptually, the osmotic diuretic mechanism would be predicted to have the greatest efficacy in conditions wherein the BBB is uniformly intact, the entire brain retains its blood flow, all areas of mass effect also maintain intact capillary wall integrity and blood flow, and all excess fluid resides in the interstitial space. No such conditions exist. In the absence of hard data for guidance, the most judicious use of mannitol for intracranial hypertension would seem to be as follows: (1) Initiation of treatment only once elevated ICP is demonstrated or highly suspected (no

"prophylactic" or expectant usage). (2) Fastidious avoidance of hypovolemia, hypotension, and electrolyte depletion via careful volume status monitoring, ongoing isotonic fluid replacement, continuous blood pressure monitoring, and frequent (every 6 h) electrolyte assessments with ongoing repletion. (3) Frequent (every 6 h) assessment of serum osmolarity when repeated doses used, with repeat doses adjusted to a target osmolarity of 300–310 mOsm with an upper limit of 320. (4) The clinician can be reasonably justified in trying mannitol for virtually any etiology of elevated ICP.

Also ill-addressed is whether mannitol has the potential to worsen outcomes in some conditions. In massive hemispheric ischemic stroke, for example, mannitol, which dehydrates vascularized tissue, might worsen herniation by dehydrating non-infarcted brain more than the infarct and causing greater tissue shift *(157,158)*; however, this effect has not been found when sought *(159)*. Until randomized prospective trials are undertaken of specific osmotic regimens for specific intracranial conditions, this issue will remain unresolved.

Other Osmotic Compounds. Other osmotic agents have been used to the same effect, but have in large part have been abandoned in clinical practice, at least in the United States. Glycerol, a simple triol, can be administered either orally or intravenously, and does produce a decrease in ICP similar in magnitude to that of mannitol; however, it is inferior to mannitol in several respects: it has a much more frequent and severe rebound effect, it frequently produces hyperglycemia, and it causes hemolysis when used in the clinically effective range *(154,160)*. Despite these drawbacks, there is a possibility it may after further study find use as a complement to mannitol *(161)*. Sorbitol, like mannitol, can only be administered intravenously, also produces hyperglycemia, and has a duration of action of only 1–2 h (vs mannitol's 4–6 h) *(160)*. Urea is only of historical interest; it has a profound rebound effect, it produces nausea, vomiting, and diarrhea, it can generate a significant coagulopathy, and extravasation produces tissue necrosis *(162)*.

Hypertonic Saline. Hypertonic saline has received considerable attention recently for its capacity to reduce elevated ICP. Hypertonic saline (HS) began being studied in the late 1980s as a resuscitation fluid for hemorrhagic shock, with the rationale that relative to fluid resuscitation with a given volume of isotonic fluid, the same volume of hypertonic fluid results in a much greater increase in intravascular volume by drawing water from tissue *(163,164)*. It became apparent that patients in early traumatic shock trials who also had head injury fared better when given HS *(165)*. While successful hemodynamic resuscitation is critical to survival and optimization of outcome in traumatic brain injury *(166)*, it appears that there is an effect independent of successful resuscitation *(165)*. The most obvious interpretation has been that HS dehydrates brain via the same osmotic mechanism attributed to mannitol; offered in support of this argument is that the reflection coefficient of brain capillaries for sodium is 1.0 (vs mannitol's 0.9) *(163,164)*. This has led to study of hypertonic saline for the full range of patients with intracranial hypertension and cerebral edema, not merely head injured ones.

While animal model experience is now relatively extensive and shows great promise *(164)*, publication of human subject trials is unfortunately quite limited. Several case series *(156,167–169)* have consistently reported that in patients with severe traumatic brain injury and ICP more than 25 mmHg refractory to standard supportive care, mannitol, and (in most patients) barbiturate coma, hypertonic saline boluses reduced ICP to within normal range. Whereas in the 24 brain-injured patients reported in these works the response rate was 100%, publication bias precludes assessment of true response rate in such circumstances. Two case series have reported the use of HS as a maintenance fluid to produce a constant hypertonic state. One reported experience with 8 head injured, 5 postcraniotomy, 8 intracerebral hemorrhage, and 6 ischemic stroke patients *(170)*, suggested that continuous infusion of HS to maintain serum sodium of 145–155 mmol/L is safe and effective at lowering ICP, although more so for TBI and post-op patients than for the two stroke groups. The second reported a case series of 68 selected pediatric head injury patients who received HS infusion titrated to whatever serum

sodium was necessary to produce ICP less than 20 mmHg, as part of a protocol including head elevation, sedation, hyperventilation, mannitol, and barbiturates. The authors concluded that hypertonic saline appeared safe and effective in their patients. Only two clinical trials have been reported. The first reported in-the-field resuscitation of 34 adult head trauma patients randomized to either lactated Ringer's solution (LR) or hypertonic saline *(171)*. No differences in outcome were detected between the groups, and the HS treated patients required more treatment interventions; the study was confounded, however, by more severe degree of injury in the treatment group than the LR-treated placebo group, and the data did suggest efficacy against elevated ICP despite showing no improved outcome. The second trial reported 35 pediatric head trauma patients randomized to either LR or HS maintenance fluids over the first 72 h in hospital *(145)*; whereas no differences in ICP and no differences in mortality were detected, the HS-treated patients had shorter ICU stays, lower rates of infectious and metabolic complications and a lower rate of development of ARDS.

Hypertonic saline is not without potential adverse effects. Although the specter of central pontine myelinolysis occurs to many neurologic clinicians, this appears to be related to antecedent hyponatremia and has yet to be reported in traumatic shock or intracranial hypertension patients treated with HS. Subdural hemorrhage and seizures are also theoretical complications of sudden electrolyte shifts *(164)*, but also have not been reported; nor has a rebound effect on intracranial hypertension yet been observed. Theoretical systemic adverse effects include volume overload, renal failure, coagulopathy, hypokalemia, and hyperchloremic metabolic acidosis *(164)*; of these, only the first two have been observed in the reports discussed previously, but whether they were deliberately sought cannot be assessed with confidence.

In summary, hypertonic saline is a treatment modality which appears to show great promise for treatment of intracranial hypertension, but is likely "not quite ready for prime time." Although it appears that judicious approaches to its use, such as careful titration of the serum sodium to a slight degree of hypernatremia (e.g., 145–150 mmol/L), may produce salutary effects on ICP, even this use cannot yet be supported on the basis of the available literature. As has been observed elsewhere in this chapter, though, these same criticisms can be justly made of the accepted standard of care, to wit, mannitol. Given the robust response reported by several authors and the lack of reported complications, it does seem justifiable at this point to consider HS an option in patients with elevated ICP refractory to all other measures. Optimally, we would like to see trials that compare the use of NS to mannitol for various specific conditions.

Acetazolamide. Carbonic anhydrase inhibition at the choroid plexus, when accomplished with sufficiently high doses of acetazolamide, can produce greater than 99% reduction in the rate of production of CSF *(172)*; unfortunately, as the derangement in CSF dynamics (if any) in most instances is an increased resistance to resorption, acetazolamide produces little effect on increased ICP in most pathologic states *(13)*. The single exception appears to be pseudotumor cerebri, which is rarely life-threatening. Recent negative results of trials of acetazolamide and furosemide for hydrocephalus after intraventricular hemorrhage in infants reinforce this view *(173–175)*.

Loop Diuretics. Loop diuretics are considered to be a therapeutic option for intracranial hypertension by some *(47,56)*, but not by others *(10,14,21,175)*. All authorities agree that loop diuretics are of minimal use when used alone *(47,56,176)*. Furosemide when co-administered with mannitol certainly produces a more profound diuresis *(177)*; it may act as a carbonic anhydrase inhibitor at the choroid, potentially decreasing CSF production *(172)*. Whether these mechanisms produce a more effective dehydration of brain, and if so for what duration, is unknown *(176)*. It seems reasonable to consider loop diuretics an option in patients with impaired myocardial contractility, who may respond poorly to the increased myocardial work resulting from the increased intravascular volume of a bolus of mannitol or hypertonic saline; however, their use alone or as a routine adjunct to hypertonic agents cannot be recommended. When they are used, meticulous care must be taken to ensure that hypovolemia does not ensue.

Steroids

While their underlying physiologic mechanisms of action remain an area of unresolved inquiry *(178)*, it is a fact of clinical certainty that glucocorticoids have potent efficacy against the cerebral edema associated with tumors. Contrary to the therapeutic enthusiasm that followed that discovery, however, it appears that their use is minimally beneficial or actually harmful when used for most of the other diagnoses listed previously.

Glucocorticoids are clearly beneficial to patients with intracranial tumors, both primary and metastatic. Focal neurological signs and decreased mental status due to surrounding edema typically begin to improve within hours *(179)*; increased ICP, when present, decreases over the following 2–5 d, in some cases to normal *(180,181)*. The exact cellular mechanisms by which peritumoral vasogenic edema is reduced remain unknown. The most commonly utilized regimen is intravenous dexamethasone, 4 mg every 6 h, but methylprednisolone can be substituted. Dose is often titrated to response. Decision making with regard to timing of excision is beyond the purview of this book, and the interested reader is referred to textbooks of oncologic neurosurgery.

The nearest comparable condition to brain tumor is brain abscess, in which a mass lesion is surrounded by vasogenic edema; however, the therapeutic usefulness of steroids for abscess is unclear. Experimental results demonstrate no improved outcome, nor do they show alteration in parameters which would be expected to improve outcome *(182–184)*; though these studies have not assessed ICP. A single small but well-reasoned radiologic report does suggest that steroids can reduce the amount of edema surrounding the abscess capsule *(185)*; extrapolation from the literature would suggest that this could translate into decreased ICP, but data are lacking. No trials have been done. Some authors argue that reducing peri-abscess inflammation with steroids may worsen outcome by decreasing delivery of antibiotics to the infected area *(186,187)*. Many authors *(81–84)* therefore recommend that if steroids are to be used at all, they be reserved for cases in which mass effect is producing life-threatening herniation, and that they be weaned off as soon as possible. In all cases, steroids are most certainly a mere adjunct to definitive antibiotic and surgical management (*see* discussion in Chapter 29).

A similar state of affairs exists with neurocysticercosis: no trial data are available, and there are arguments to be made both for and against the use of glucocorticoids *(188)*. Given this state of affairs, it seems prudent to reserve steroid use to patients with a high lesion load in whom the pericystic edema is sufficient to produce elevated ICP or a dangerous degree of herniation. As with bacterial abscess, surgically remediable situations (particularly, obstructive hydrocephalus) should be treated appropriately, and definitive antiparasitic treatment initiated as soon as possible (*see* Chapter 29).

Postinfectious encephalitis has been reported to respond favorably to steroids in some cases *(189)*; more systematic evaluation is needed. Multiple reports of treatment of herpes simplex virus (HSV) encephalitis with high-dose corticosteroids were made in the early 1970s *(190–192)*, and arguments have been made both for and against conceptual grounds. The controlled trials to answer the issue have never been carried out. Multiple subsequent reports of HSV encephalitis precipitated by steroid treatment have quelled enthusiasm for their use in less severely affected patients, and most modern authors who advocate their use do so only for patients in whom ICP is thought to be critically elevated *(193–194)*. The best evidence available comes from Whitley and associates' trial comparing vidarabine to acyclovir for HSV encephalitis *(195)*. Approximately one-third of patients in each treatment group received steroids, and a regression model found that steroid treatment did not contribute significantly to outcome (i.e., steroids neither helped nor hurt). No analysis was done, however, on the subset of patients with low GCS, who were most likely to have a large degree of swelling and hence raised ICP; therefore, even these data do not bear on the question as to whether the sickest of the sick would have anything to gain from steroid treatment. The clinician is therefore left to make his or her best guess, with no data for guidance.

Extensive study has been given to the use of steroids for meningitis *(196–201)*. It is clear that they decrease the frequency of deafness and other neurologic deficits in children (and possibly also in adults, though this is less clear). For reasons of improved neurologic outcome, therefore, corticosteroids are now standard of care in pediatric meningitis patients, and an option in adults (*see* Chapter 29). However, it is important to note that mortality rates have been unchanged in studies to date.

The best evidence available strongly suggests that there is no benefit from glucocorticoids in traumatic brain injury *(202,203)*, intracerebral hemorrhage *(204)*, or ischemic stroke *(205–208)*. While there are reports of high-dose steroids preventing vasospasm in SAH *(209–211)*, this use can only be regarded as experimental until a properly conducted trial is published.

For some of the other conditions listed Table 1, the use of glucocorticoids is advocated by some authors with very little in the way of supportive evidence available (*see* the High-Altitude Cerebral Edema section). Until better studies are published, we advise extreme judiciousness in their use for conditions other than brain tumors and possibly the various infectious conditions already discussed. The potential deleterious consequences of their use—hyperglycemia, agitation, peptic ulcers, immunosuppression, wound breakdown—dictate that they be utilized only when there is confidence that they will produce an improvement in outcome. Steroids were used widely and confidently for both ischemic stroke and head injury until well-conducted trials demonstrated no benefit. This experience should dictate a skeptical view toward their use in other conditions for which supportive evidence is lacking.

Anesthesia

Barbiturates. Although it took years to gain in popularity from its introduction in the late 1960s, generalized anesthesia with "barbiturate coma" has become an accepted option in the treatment of intracranial hypertension. The putative mechanism behind the decrease in ICP induced by barbiturates is a reduction in cerebral metabolic activity, leading to reduced CBF and CBV *(212,213)*. There is little doubt that in most patients, induction of barbiturate anesthesia produces an immediate drop in ICP, sometimes profound. What is far less certain is in which patients are their ultimate outcome improved by the intervention.

The clinical circumstance for which barbiturate coma is most supportable is head trauma. Eisenberg and associates' 1988 trial of pentobarbital for severe head injury established with reasonable certainty that induction of barbiturate coma has the potential to improve outcomes in a selected subpopulation of these patients *(214)*. In light of the negative results of other trials *(215,216)* in which barbiturates were used on a prophylactic basis, together with reported experiences of nonrandomized patient series *(212,217)*, the best balance between benefit from lowered ICP and the adverse effects of barbiturates themselves (discussed in this section below) can be accomplished by selecting TBI patients with a GCS score of less than 8 but more than 3, who have demonstrated sustained ICP greater than 20 despite excision of mass lesions (e.g., hematoma), head elevation, sedation, hypertonic therapy, and CSF drainage if possible. The only effective gauge of therapeutic response is continuous EEG monitoring, with titration of dose to a burst-suppression pattern; further dose increases to the point of electrocerebral silence appear to produce minimal further beneficial effect on ICP with added risk of adverse effects *(213,214)*.

There is little to be gained from barbiturate coma in circumstances of mass effect such as tumor, abscess or hematoma, which require excision or drainage. This surgical imperative has essentially precluded formal evaluation of barbiturates in these conditions. Massive hemispheric stroke, which produces a volume of devitalized swollen tissue, also appears to respond poorly to barbiturates *(212,218)*, which only decrease CBV of noninfarcted tissue. Fulminant hepatic failure, by contrast, may represent a pathology in which decreased cerebral metabolism has the potential to produce improved outcome (*see* Fulminant Hepatic Failure section). There is little available in the literature

regarding the treatment of any other conditions with barbiturates, and defensible recommendations therefore cannot be made.

The adverse effects of barbiturate therapy are a significant limiting factor in their therapeutic use. Barbiturates produce an immediate and sustained depressive effect on systemic arterial blood pressure, which frequently necessitates vasopressor support if adverse consequences to CPP are to be avoided *(56,214)*; they also can produce myocardial suppression, which can be refractory to inotropes and pressors and potentially lethal. Barbiturates have a significant immunosuppressive effect, resulting in an increased risk of infection *(213,218)*. This is potentiated by the prolonged immobility and endotracheal intubation associated with induced coma. Barbiturates also tend to produce systemic hypothermia *(213)*, which may mask signs of infection *(56)*. Lastly, all barbiturate agents accumulate with prolonged exposure, and patients may remain comatose for days after cessation of therapy. Adverse consequences due to these effects must be minimized if the potential gains which barbiturate coma has to offer are to be realized. Detailed and fastidious care must be taken to optimize hemodynamic status as outlined elsewhere in this chapter; given the profound myocardial suppressive effect of these agents, many authorities *(47,56)* recommend the placement of a Swan-Ganz pulmonary artery catheter with frequent assessment of volume status and myocardial function, and titration of vasopressors and inotropic agents (e.g., dopamine and dobutamine) as necessary. Nursing must also aggressively monitor for any possible supervening infections and the development of decubitus ulcers, and deep venous thrombosis prophylaxis should be scrupulously applied.

There is a fair degree of concensus among recent reviewers regarding preferable regimen for the induction of barbiturate coma *(10,14,39,56,176,219)*: pentobarbital, administered as a bolus, followed by a continuous infusion of 0.5–3.0 mg/kg/h titrated to a burst-suppression pattern on EEG or normalization of ICP, whichever is achieved first. These effects are generally achieved at serum levels of approx 3 mg/dL *(10,176)*. Recommendations regarding the initial bolus itself vary somewhat, from 3–10 mg/kg over 30–180 min *(10)* to 5–30 mg/kg at 1 mg/kg/min *(39)*. Although there is no evidence that either thiopental or phenobarbital is less effective at suppressing cerebral activity and hence decreasing ICP, both of these agents have a longer physiologic half life than pentobarbital when given in repeated doses *(213)*; pentobarbital is therefore the preferred agent, because prolonged sedation is one of the identified drawbacks of this technique.

Barbiturate coma, when used, should be maintained for at least 48 h, or until the pathologic state underlying ICP elevation is likely to have reversed, as long as cardiovascular function permits this. Withdrawal of barbiturate coverage should be stepwise, not sudden; one reasonable approach is to decrease the hourly infusion rate by 50% each day *(56)*. (Regarding cardiovascular monitoring and the use of EEG patterns in continuous neurophysiologic monitoring, *see* Chapter 6.)

Propofol. Considerable attention has been given in the past few years to the utilization of propofol in neurointensive care, due to its brief duration of action and short washout period *(220,221)*. These features contrast to benzodiazepines and barbiturates, whose washout period is much longer, significantly complicating attempts to periodically discontinue sedation to assess neurologic functioning. Propofol has therefore seen use in neurointensive care as a sedative agent when frequent neurologic assessment is desired.

This application may also extend to the control of intracranial hypertension. Propofol produces a significant drop in ICP in patients with normal intracranial dynamics, with preserved CPP *(222,223)*, apparently because of the same fall in cerebral metabolic rate and, hence, CBF produced by barbiturates *(224)*. This effect is preserved in patients with increased ICP after head trauma *(225)*. The therapeutic use of this effect has been assessed in a single trial of propofol sedation of patients with head injury *(226)*. The chief achievement of this trial was to demonstrate the safety of prolonged use of propofol (mean time on propofol 95 h) in these patients. Propofol-treated patients required less CSF drainage, had lower ICP on day 3 of the study, and required less use of other pharmacologic interventions than did controls; these encouraging findings and equivalent outcome were despite a

higher prevalence in the treatment group of negative predictive variables (greater age, lower GCS, more likely to have had early hypoxia or hypotension). However, this single trial was small (42 total patients) and did not demonstrate any improvement in outcome. Unfortunately, there are even less systematic data available pertaining to the prolonged use of propofol for any other etiology of elevated ICP. The same criticism, however, can be legitimately made of barbiturates.

Propofol does have significant adverse effects that must be carefully accounted for if its potential benefits are to be realized (*see also* Chapter 12). It has a profound hypotensive effect, and vasopressors very frequently must be coadministered *(220)*. Although previous evaluation has demonstrated that concurrent decrease in ICP is sufficient to produce a preservation of CPP despite systemic hypotension, prudence dictates that strict measures be taken to maintain systemic blood pressure and that an ICP monitor be in place to verify that ICP is not unexpectedly increasing from intracranial vasodilation. One other prominent adverse effect is a predisposition to infection. Whereas early reports of Gram-negative sepsis appear to have been successfully countered by addition of the preservative EDTA to the vehicle, there nonetheless does appear to be an increased risk for nosocomial infection while maintained on propofol sedation *(220,226)*, and any patient so maintained must be carefully watched for any signs of infection. This increased tendency cannot be considered a contraindication to propofol's use in appropriate circumstances, as the same increased risk is present with barbiturate sedation. Comparison of the relative rates on each agent awaits clarification in future trials. Other adverse effects or propofol which must be borne in mind are due to the lipid emulsification vehicle, and include hypertriglyceridemia, more likely in the elderly, and increased CO_2 production *(220)*. Serum lipids may be monitored periodically, any indication of pancreatitis watched for, and nutritional supplementation should be adjusted downward to account for the lipid and calorie content of the vehicle. Rare cases of metabolic acidosis, apparently idiosyncratic, have been reported, some of them fatal *(227)*. Lastly, a recent review has called into question whether propofol has the potential for epileptogenicity in some patients *(228)*; we are skeptical of such an association, as we have not seen it in many patients treated with propofol, but pending the publication of better data, this possibility must be borne in mind if a patient started on propofol begins to seize, and continuous EEG monitoring should be seriously considered if propofol anesthesia is to be used safely.

At this time, therefore, the use of prolonged propofol sedation for amelioration of intracranial hypertension can be considered a legitimate practice option, provided that the possibilities of acidosis and seizure are borne in mind and monitored for. Propofol sedation should be undertaken in the same circumstances in which barbiturate coma is pursued: intracranial hypertension refractory to general supportive management as outlined previously, surgical evacuation of mass lesions, and hyperosmotic therapy; additionally, in certain circumstances, its short duration of action may render it a legitimate short-term therapeutic option while definitive surgery is being arranged, provided that systemic blood pressure is scrupulously maintained and ideally with an ICP monitor already in place.

Other Anesthetic Agents. Other sedative-hypnotic agents bear mention only in passing. The routine use of benzodiazepines and opiates in the neuroscience intensive care unit is considered in Chapter 12; these agents' only role in the control of intracranial hypertension is to maintain quiet sedation, avoiding surges in ICP owing to agitated motor activity and "bucking" the ventilator. Etomidate is effective at reducing cerebral metabolic rate and cerebral blood volume, but is a potent inhibitor of steroidogenesis, producing adrenal insufficiency with repeated dosing, and its use is therefore contraindicated in any context other than rapid-sequence intubation or anesthetic induction. Anesthetic gasses (nitrous oxide and the halothanes) have the potential to increase cerebral blood flow profoundly, increasing ICP, and therefore can only be used safely if at all during craniotomy, not in the ICU.

Ketamine deserves special mention as an agent with the potential for future use. Formerly considered absolutely contraindicated in patients with the potential for elevated ICP *(221)*, ketamine has been demonstrated in two recent reports *(229,230)* to have no significant effect on ICP in head injured

patients who were under sedation (with propofol in one report and midazolam or fentanyl in the other). In the one study with a control group, ketamine's sympathomimetic properties were found to decrease the need for vasopressors, resulted in a higher average CPP, and promoted intestinal motility in patients on opiates *(230)*. As a result of the small numbers studied (43 total) in these reports, it is too early to advocate ketamine's use, but with further study, it may come to play a role in the support of patients requiring heavy sedation for critical intracranial illnesses.

Pharmacologic Paralysis

The use of neuromuscular blockade paralysis has been advocated by some in the treatment of patients with dangerously elevated ICP, generally for the stated purpose of abolishing surges in ICP (especially plateau waves) that are induced by coughing or other such Valsalva equivalents *(39)*. At one time, this measure was considered routine, standard feature or the treatment of patients with severe head injury at many centers; however, recent retrospective analyses have demonstrated *higher* likelihood of elevated ICP *(231)* and worse rates of disability *(232)* in traumatic brain injury patients treated with neuromuscular blockade. No prospective trial has ever been conducted in any condition. There is no doubt that this technique can be successful in blunting surges in ICP provoked by endobronchial suctioning *(233)*. The wisest course of action therefore seems to be that if neuromuscular blockade is used at all, it be used only in patients who have a demonstrated propensity to surges of ICP associated with specific situations such as bronchial suctioning, and then only for limited periods of time. Nondepolarizing agents must be used, as succinylcholine has the potential to directly increase ICP through the muscle contraction it produces *(234)*. Unless absolutely necessary, use should probably be avoided altogether in any patient on glucocorticoids, given the potential of paralytic agents and steroids together to potentiate critical illness myopathy *(235)*.

Indomethacin

There have been several reports since 1991 of a possible ICP-lowering effect of intravenous indomethacin. Aside from a single case report in a patient with fulminant hepatic failure and renal failure (who later died despite the observed effect) *(236)*, the patients have all had traumatic brain injury *(237–239)*. Animal data have suggested that indomethacin can produce a fall in CBF *(240)*. Those reports that permitted observation support a similar effect in traumatic brain injury patients *(237,239)*. Another possible mechanism in injured patients is reduction or prevention of fever, which was definitely seen in one patient series *(237)*, and possibly in another *(238)*. Until a larger trial is published, especially given the potential for indomethacin (like all high-dose nonsteroidal anti-inflammatory agents) to produce peptic ulcers, indomethacin must remain an agent with promise whose use cannot yet be recommended.

Hypothermia

The induction of systemic hypothermia has been shown to produce multiple salutary chemical and histologic effects in animal models of various acute intracranial processes. For the most part, unfortunately, these findings have not been translatable into improved outcomes in human trials.

The single exception to this is in the treatment of diffuse ischemic brain injury after cardiac arrest. Two simultaneously reported trials *(241,242)* recently investigated the effect of systemic hypothermia induced by external cooling in adults who suffered out-of-hospital cardiac arrest, with ventricular fibrillation as the first recorded rhythm, in whom spontaneous circulation was restored, who were comatose initially after return of circulation. Hypothermia to a temperature of about 32°C was accomplished within 8 h in both trials, maintained for 12 h in one study and 24 h in the other, and followed by passive rewarming. Overall survival was improved in the larger study, and survival to independence was improved in both. The chief limitation of these studies is the narrowly defined patient group: all patients had ventricular fibrillation arrest, almost all of cardiac origin; bystander CPR was performed in the majority; and time from collapse to return of spontaneous circulation was

less than 25 min in the majority. It is estimated that less than 20% of patients with out-of-hospital arrest fit the inclusion criteria of these studies *(243)*. It is also important to note from the standpoint of treatment for intracranial hypertension that none of these patients had ICP monitors; therefore, it is unclear how many if any had sufficient brain swelling to increase ICP. Pending publication of any "negative" trials, however, it appears that induced systemic hypothermia improves outcome in a limited subset of patients with postarrest diffuse ischemic brain injury.

The role of hypothermia in the treatment of head injury is less clear. The recent completion of the National Brain Injury Study: Hypothermia trial *(244)* appears to emphatically confirm smaller trials' findings *(245,246)* that induced hypothermia for unselected patients with severe head injury does not improve long-term outcome. However, this finding is at odds with a large volume of animal literature *(244)*, as well as findings of at least one other trial of size *(247)*. Moreover, it remains possible that hypothermia may be beneficial when instituted only for those head-injured patients with demonstrated intracranial hypertension *(248)*. At present, the conservative interpretation of the available data is that the adverse effects of systemic hypothermia outweigh the benefits on intracranial dynamics, and that this treatment does not benefit unselected patients with severe head injury *(249)*. However, the large body of work suggesting potential benefits to some patients (particularly those with established tendency toward elevated ICP) is sufficiently compelling that some practitioners continue to utilize this measure *(250)*. The clarification of which subgroups of patients would benefit from hypothermia awaits the publication of further trials. Preliminary trials of hypothermia in acute ischemic stroke have been encouraging *(251–253)*, but this must be regarded as an experimental therapy until larger trials are published.

To date, all trials of systemic hypothermia have utilized external cooling (endovascular devices may have a future role, but are currently experimental *[254]*). Most trials have used water-circulating *(245,246,248,251–253)* or air-circulating *(241)* cooling blankets to achieve hypothermia; other means have included surface ice packs *(241,242,244)* and iced gastric lavage *(244,245)*. It appears that water-circulating blankets have slightly greater speed and efficacy vs other techniques, and are certainly the most convenient; however, surface ice packs and iced gastric lavage depress temperature only slightly less rapidly, and are readily available in all medical centers. Current concensus regarding the target body temperature is 32–34°C. Most trialists agree on the use of urinary bladder catheter thermistors for measurement of core body temperature. In most trials, shivering has been controlled with neuromuscular blockers *(241,242,244,245,251–253)*. As noted, the trials for postarrest coma maintained hypothermia for between 12 and 24 h after initiation; guidelines regarding duration of cooling for head trauma and stroke cannot be offered. There is no concensus regarding whether rewarming should be active (induced with an external device) or passive (spontaneous metabolic reequilibration on the patient's part).

Several potential complications of hypothermia must be actively guarded against if any therapeutic utility is to be realized. The absence of statistical significance in the postarrest trials *(241,242)* notwithstanding, the aggregate experience across human trials is highly suggestive of an elevated rate of infection, especially pneumonia *(249)*. Any patient in whom hypothermia is induced must therefore be monitored fastidiously for infection. Given that fever cannot be assessed, and given the high rates with which infection has been seen in some trials *(246)*, the prophylactic administration of broad-spectrum antibiotics is likely a defensible course of action, though this intervention has not itself been subjected to a trial. The second metabolic derangement classically associated with hypothermia, coagulopathy *(255,256)*, has remained more consistently nonevident in trials of therapeutic hypothermia, suggesting that it is less a primary effect of hypothermia itself than of other associated conditions, such as trauma, in whose company it has been seen. Nevertheless, careful attention to coagulation times and monitoring for hemorrhagic complications is warranted. Serum electrolytes, particularly potassium, magnesium, calcium and phosphate, can drop rapidly and significantly during the cooling phase *(257)*; electrolyte levels should be frequently assessed and repleted, and pro-

phylactic administration may be of utility. The necessity of neuromuscular blockade to prevent shivering represents a significant potential source of iatrogenic complications (*see* Pharmacologic Paralysis section). A pharmacologic alternative to paralysis has been reported: coadministration of buspirone 30 mg enterally with moderate-dose (target serum level 0.4 μg/mL) meperidine parenterally was demonstrated to lower the shivering threshold to 33.4°C, 2.3°C below normal and significantly lower than either drug alone *(258)*. This approach has advocates in the field (S. A. Mayer, personal communication), but we are hesitant to recommend it until reports of its safe use in neurocritically ill patients are published.

Currently, then, induced systemic hypothermia is a measure appropriately utilized for selected patients initially comatose after cardiac arrest. Other uses await further trial evaluation before they can be considered proven.

Hyperbaric Oxygen

A single English-language trial *(259)* reported increased survival in head-injured patients treated with hyperbaric oxygen (100% oxygen at 1.5 atm) for 1 h every 8 h, but survival with good outcome was identical between treated and nontreated patients (i.e., the margin of increased survival between treated and nontreated patients was entirely composed of patients with dependent or vegetative outcome). Fraught with potential complications as this therapy may be *(260)*, further investigation may nonetheless prove fruitful *(261,262)*.

THAM

Tris-hydroxymethyl-aminomethane (trometamol, tromethamine, THAM) is a buffer with a pKa of 7.8; after parenteral administration, it distributes rapidly into the extracellular fluid spaces of the body, then slowly into most intracellular spaces, including the brain, and acts as a proton acceptor, buffering acidotic states—both generalized (e.g., diabetic ketoacidosis) and focal (e.g., ischemic lactic acidosis) *(263)*. Originally introduced in the early 1960s, its use for generalized acidoses was negatively received *(264)*, and it has seen little use in the United States since. Elsewhere, particularly in northern continental Europe, it has been considered a standard therapeutic intervention for elevated ICP. By maintaining pH near physiologic, even in areas of profound oxygen depletion and cytotoxic edema, THAM can ameliorate secondary cellular damage. It has been shown to decrease the water content (and thus, presumably, swelling) of traumatized brain in patients *(265)*, and to decrease both size of infarct and swelling thereof in animal models *(266,267)*. In the one English-language randomized controlled trial of THAM for head injury, THAM-treated patients had significantly lower ICP at some stages of treatment, and were significantly less likely to require barbiturate anesthesia to control ICP; the outcomes in this trial, however, appeared to favor patients who did not receive THAM, though this did *not* achieve statistical significance *(268)*. (This is a sobering realization vis-a-vis the many other treatments already discussed whose effects on ICP are known with confidence, but that have never been proven to improve outcomes in a randomized trial.) On the basis of the evidence currently available in the English-language literature, therefore, the use of THAM cannot be recommended; it remains possible, however, that future publications may necessitate reversal of this stance.

Neuroprotection

Despite multiple therapeutic agents having shown promise in animal models, to date all trials of agents intended to protect nervous tissue from the consequences of ischemia or the harmful secondary sequelae of CNS trauma have shown no benefit in humans *(269,270)*. The robustness of treatment effects in some animal paradigms renders the failure of crossover into clinical trials all the more frustrating. It is to be hoped that future evaluations may yet bear fruit.

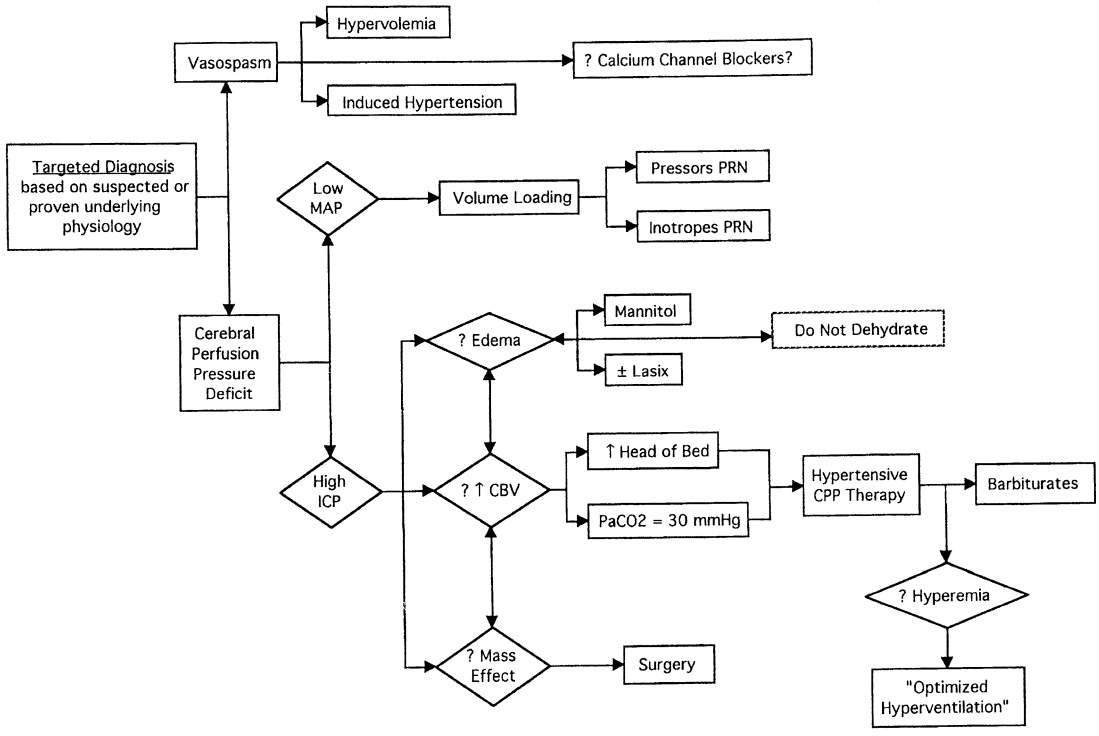

Fig. 5. ICP treatment algorithm. Developed for treating elated ICP resulting from head injury, this algorithm is derived from the physiologic principles discussed earlier in this chapter, and the "cerebral perfusion pressure deficit" arm can be conceptually applied to most pathologic states. Low arterial pressure (MAP) will produce intracranial vasodilation and potentiate A waves, and thus should be addressed with iso- or hyper-osmotic volume loading. Tissue edema may respond to mannitol or hypertonic saline. Mass effect that is surgically remediable must be addressed. Cerebral venous distention (venous CBV) must be avoided by positioning the head up 30°C; arterial CBV will respond transiently to hyperventilation. Although far from perfect, this algorithm offers a first attempt at rationalizing the use of interventions for specific pathophysiologies. Reprinted from ref. *56* with permission.

Summary

The range of therapeutic options available to the clinician dealing with a patient with brain edema or the potential for elevated ICP is thus at once both terribly narrow and dizzyingly broad. The work has yet to be done that permits clinicians to utilize them in specific disease states on a rational basis. For some clinical problems, collective clinical experience has provided enough knowledge that specific physiologically based protocols for intervention can be ventured—Fig. 5 offers an example suggested for use in severe traumatic brain injury. Hopefully, such protocols will be constructed for other disease states in the future.

This ends the review of specific interventions for brain edema and elevated intracranial pressure. The application of these interventions for most of the specific disease states already mentioned is covered in dedicated chapters elsewhere in this book; this chapter concludes with brief consideration of a few conditions not discussed elsewhere. Before concluding this section, however, it is appropriate to again note the dearth of good scientific evaluation of our therapeutic armamentarium for most

Table 4
Stages of Hepatic Encephalopathy

0	Normal function or minimal subtle neuropsychological impairment, with preserved attention span
I	Euphoria, anxiety, or depression; mild confusion; shortened attention span
II	Lethargy; disorientation; moderate confusion, impaired cognition, and inappropriate behavior
III	Somnolence or semistupor, with preserved arousability; profound confusion; purposeful response to noxious stimuli
IV	Coma, with nonpurposeful or absent response to noxious stimuli

Adapted from refs. *276* and *285*.

of the conditions we treat. Too many publications have reported on the results of particular interventions in a heterogeneous group of patients *(134,271)*. One implication of such reports is that the pathophysiology of intracranial hypertension is the same between different disease states. It is not. The field will only move forward with the publication of trials evaluating specific interventions for specific disease states, and focusing on real outcomes instead of physiologic markers presumed to be associated with outcome. There is much work to be done.

TREATMENT OF SELECT SPECIFIC ETIOLOGIES

Hepatic Failure

Defined by general concensus as progression from normal to critically impaired hepatic function within less than 8 wk, fulminant hepatic failure (FHF) once carried a dismal prognosis. With the advent of orthotopic liver transplantation, however, prospects for patients so affected are dramatically better than they once were. Because 80% of patients dying with FHF die of generalized cerebral edema and brainstem compression *(272,273)*, optimization of outcome in FHF and proper timing of liver transplantation require fastidious management of the deranged intracranial dynamics that result from profound impairment of hepatic function. Although these patients are generally cared for in medical or surgical ICUs, neurologists and neurosurgeons may be consulted to aid in the management of ICP during the acute phase of illness. Those who participate in the care of such patients frequently will wish to reference other reviews as well *(272,274–276)*.

Clinical Manifestations and Diagnosis

The manifestations of hepatic encephalopathy are in most respects those of any toxic-metabolic encephalopathy. Many patients with hepatic disease will have milder degrees of encephalopathy as their initial presenting complaint. A clinical grading system has been devised (Table 4) to permit ease of communication between clinicians caring for these patients, and as part of a broader grading of severity of disease, the Child-Turcotte-Pugh score (Table 5) *(277)*. The diagnosis of hepatic encephalopathy is straightforward in any patient presenting with cognitive impairment in the setting of clinical manifestations of hepatic disease (e.g., visible jaundice, diffuse itching, abdominal pain) and can be considered established with the demonstration of impaired hepatic function on standard laboratory liver function tests (Table 6) without clinical or laboratory evidence of other causes of encephalopathy. The presence of asterixis, an intermittent loss of muscle tone in any muscle group engaged in sustained antigravity exertion *(278)*, is supportive; however, asterixis is not specific to hepatic encephalopathy *(279)*, and care must be taken to exclude the presence of uremia and hypercarbia. The presence of triphasic waves on EEG is likewise supportive, although this finding also can be present in other encephalopathies, may be demonstrable in only 25% of patients with confirmed hepatic encephalopathy, and may degrade to nonspecific delta coma with progression to stage IV encephalopathy *(280)*.

A distinction is generally made between patients with chronic, mild- to moderate-severity hepatic impairment, and those with severe, rapidly advancing, FHF. In general, chronic states are far better tolerated by the brain than is FHF. Even in patients with longstanding cirrhosis, however, sudden

Table 5
Child-Turcotte-Pugh Score

Points	1	2	3
Encephalopathy	None	Stage I–II	Stage III–IV
Ascites	Absent	Slight	Moderate–severe
Bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (s)	<15	15–17	>17

decompensation of hepatic function has the potential to induce sufficient derangement of brain metabolism that diffuse brain edema develops *(281)*.

Establishing the diagnosis of FHF-associated brain edema is as simple as demonstrating characteristic findings on neuroimaging (diffuse gyral swelling, increased water content of white matter, abolishment of CSF spaces) in the appropriate clinical context. Seventy percent to 80% of patients who progress to stage IV hepatic coma will have such brain swelling *(272)*.

Pathophysiology

The cellular metabolic substrates of elevated ICP in hepatic failure remain a subject of controversy. Much attention has been paid to the role of hyperammonemia in hepatic failure *(282)*, and the argument has been advanced that resulting increases in intraglial glutamine induce cytotoxic edema *(275,283)*. One difficulty with this theory is that chronic hepatic impairment can result in the same apparent degree of ammonia-glutamine elevations, without inducing the same degree of cerebral edema *(275)*. Other factors appear to be at play as well, including impaired sodium-potassium ATPase function *(284)*.

Whatever the underlying biochemical substrate, the end result of FHF to the brain is diffuse cerebral edema, predominantly due to cellular swelling *(274,275)*. This can reach sufficient degree to produce tonsillar impaction, or diffuse elevation of ICP, abolishment of CPP, and devastating diffuse ischemic injury *(274,275)*. A tenuous intracranial system may be further destabilized by other systemic metabolic derangements which result from hepatic failure; specifically, failure of hepatic gluconeogenesis can lead to neurotoxic hypoglycemia, and the development of pulmonary arteriovenous shunting (hepatopulmonary syndrome) can produce systemic hypoxia *(285)*. These patients also often develop renal failure, which, while not necessarily directly neurotoxic, can significantly complicate management.

Treatment

Definitive treatment of FHF depends on identification and reversal of the inciting hepatic injury with restoration of function, and failing that goal, liver transplantation. Liver transplantation eligibility is a complex and evolving decision-making process; as this is the province of hepatologists and transplant surgeons, interested readers are referred elsewhere for discussion *(277)*.

In every patient with stage III or IV hepatic encephalopathy, all standard medical measures for intracranial hypertension should be taken (positioning, temperature, avoidance of hypotonic fluids, avoidance of agitation or Valsalva, volume repletion and BP support). Serum glucose must be frequently, vigilantly monitored, and intravenous dextrose administered when necessary, in as hypertonic a solution as possible. Any significant decrement in neurologic status should prompt head CT to evaluate for intracranial bleeding, which if detected should prompt redoubled efforts at reversal of coagulopathy, and appropriate surgical intervention. Steroids appear to have no salutary effect, and may possibly be detrimental *(39)*. Sedative use should be judicious, given the prolonged clearance that hepatic impairment produces, but should nonetheless be instituted in agitated, combative patients. Most published accounts report proceeding with elective intubation once patients progress to

Table 6
Laboratory Abnormalities Suggestive of Hepatic Impairment

Elevated bilirubin
Elevated ammonia
Elevated transaminases (AST [SGOT], ALT [SGPT])
Elevated prothrombin time
Decreased albumin

ALT [SGPT], alanine transaminase; AST [SGOT]; aspartate transaminase.

stage III encephalopathy *(272,286)*. Other medical measures for ICP control should likely be utilized only in titration to directly measured ICP, and are discussed below in this section.

Authorities disagree about the issue of invasive ICP measurement. The impressive experience reported by Lidofsky and colleagues *(272)*, using a standardized CPP-targeted approach including invasive monitoring in every patient, has proven convincing to many *(274,275)*. Others *(247)*, however, report that in their hands invasive monitoring yielded insufficient treatment-altering information to justify the risks of monitor placement. It must be admitted that invasive ICP monitoring has not been conclusively demonstrated to change patient outcome. A pessimistic reading of previous patient series' findings of universally poor outcome in patients who developed elevated ICP *(287,288)* would be to conclude that once ICP elevation is documented, poor outcome is highly likely, and transplantation should no longer be offered. The current climate of organ shortage encourages such pessimism. One goal of ICP monitoring, then, could be formulated as avoidance of intracranial hypertension and neurological injury in patients whose ICP has almost but not quite yet destabilized. Another definite indication for ICP monitoring is detection and reversal of ICP surges in the perioperative context; cumulative experience *(272,289)* strongly suggests that fastidious control of ICP during transplant surgery may significantly contribute to optimizing ultimate neurologic recovery from FHF requiring liver transplantation.

If invasive monitoring is elected, coagulopathy should be reversed with FFP and platelets before device insertion, to greater than 3 s prolongation of the prothrombin time and a platelet count of greater than 50,000/mm^3 *(274)*. Choice of device is a matter of argument. Most practitioners utilize the subarachnoid bolt or an epidural device, due to their lower risks of hemorrhagic complications. Ventricular catheter use seems unwise, given the substantially higher hemorrhagic and infectious risks, especially considering that diffuse cerebral edema of FHF often leads to ventricular effacement or even abolishment, rendering IVC placement more than usually risky. Whether the increased accuracy of the Camino catheter justifies the higher hemorrhagic risks must remain a case-by-case decision.

The optimal medical means by which to treat ICP in these patients cannot be known with any degree of confidence due to a complete lack of data, and therapeutic choices thus remain empiric. Those with experience *(39,272,290)* report that mannitol retains some efficacy against the diffuse edema of FHF; while its use may induce or exacerbate renal failure, hemodialysis can be utilized to counter this *(272,291)*, permitting the osmotic dehydration of brain that is desired. (If hemodialysis is necessary, continuous venovenous dialysis is advisable, in the interests of minimizing the severity of fluid and electrolyte shifts.) The induction of barbiturate coma has been convincingly demonstrated *(212,272,292)* to reduce cerebral metabolic rate and decrease ICP in these patients. Short-term bolus administration of barbiturates can be potently useful for blunting ICP surges during surgery *(272,293)*. The best use of these agents for pretransplant ICU patients is less clear, for the simple reason that induction of barbiturate coma confounds the grading of hepatic encephalopathy. If progression to refractory stage IV is regarded as the "point of no return" beyond which transplantation is not pursued because of a high likelihood of poor neurologic outcome, then barbiturate coma should only be induced in pretransplant patients for whom an organ has been identified to minimize the chance of ICP surges during the preoperative and perioperative period. The last means of medical ICP control

that has received attention in the literature is induction of systemic hypothermia; recent reports *(294–296)* suggest that this technique is relatively safe and modestly effective at preventing or blunting ICP elevations. The relative benefits and adverse effects of hypothermia vs barbiturate administration cannot be known with any degree of confidence, and await publication.

Lastly, a note must be made regarding the subject of deliberate hyperventilation. As discussed previously, there is reason to believe both on conceptual grounds (vasoconstrictive effect is short-lived, comes at the expense of producing a rebound hyperemia, and can produce areas of focal ischemia) and patient data (demonstrating worse outcome in head-injured patients) that sustained hyperventilation is an inappropriate therapeutic modality for intracranial hypertension, and should be used only as a bridge to definitive therapy or when all other means have failed. A survey of recent publications on treatment of cerebral edema in FHF *(286,289,297)* indicates that institution and maintenance of sustained hyperventilation remains a standard component of therapy in many surgical centers. It seems unlikely that any trial of size will be undertaken to address whether sustained hyperventilation is advantageous or detrimental to FHF patients.

Outcome

Before the advent of orthotopic liver transplantation, the outcome for patients with fulminant hepatic failure was universally dismal. Contemporary patient series *(272,293,298)*; however, report survival rates ranging up to 74%. Of course, such rates depend fundamentally on how FHF is defined, and comparison of these rates for the current era vs the pretransplant era are further confounded by interim improvements in best medical management without transplantation. There can be little doubt, however, that orthotopic liver transplantation has afforded survival to some FHF patients that previously would have died. Future improvements in outcome will likely be based on (a) improving the availability of donor organs or substitutes thereto, and (b) improving the management of cerebral edema—the cause of death in 80% of those dying with FHF *(273)*.

High-Altitude Cerebral Edema

Commonly abbreviated HACE, cerebral edema in the context of recent ascent to high altitude is considered by many to be an extreme form of acute mountain sickness (AMS) *(299)*.

Clinical Manifestations

AMS, characterized by headache, fatigue, anorexia, nausea, and sleeplessness, characteristically affects those who have ascended from near sea level to 2500 m or higher, resolving over 1–3 d. Approximately 20% of those making such an ascent may be affected. HACE, by contrast, is much more severe, and much rarer. Both appear to correlate with rapidity and magnitude of ascent. HACE typically manifests first as AMS, with progression within 12–72 h of ascent to ataxia, confusion, lethargy and eventually coma; vomiting, hallucinations, and seizures have also been seen *(300)*.

Pathophysiology

Pathophysiology is incompletely understood. The diagnosis was initially appreciated on the basis of autopsy demonstration of diffuse brain swelling in those dying with the syndrome. Recent MRI data, showing that edema is limited to white matter only, have been interpreted as favoring a vasogenic mechanism *(301)*. Physiologic studies have demonstrated increased brain water and decreased brain compliance at altitude *(299)*. Awaiting clarification are why ascent to low oxygen tension environments should induce endothelial or other cellular dysfunction and what factors determine which few develop HACE while others are negligibly to merely mildly affected.

It is vital to the appropriate care of patients with HACE to also recognize the syndrome of high-altitude pulmonary edema (HAPE), which is coincident in a very high percentage of patients *(299,300)*. HAPE is characterized by a diffuse alveolar edema of high protein content, which has been taken as evidence of an underlying derangement of lung capillary permeability—(i.e., vasogenic edema in a different vessel bed; *300*). It shares the same risk factors as HACE, and is also rare.

Symptoms are dyspnea, fatigue, and a dry cough; clinical and laboratory examination reveal hypoxia, tachypnea with a respiratory alkalosis, fluffy radiographic infiltrates, and not uncommonly, a pyrexia of up to 38.5°C *(300)*.

Diagnosis

Diagnosis rests simply on recognition of characteristic clinical features in the context of ascent to altitude. MRI demonstration of edema is of interest, and may be of use in ruling out other conditions, but is otherwise not necessary for clinical management. Lumbar puncture is better avoided unless absolutely necessary to rule out meningitis, and should be done with standard measures to minimize risks of herniation—small-bore needle, slow removal of the minimal diagnostically necessary volume of CSF, and assurance of the ability to treat emergently in the event that herniation is induced (previously secured intravenous access, at-hand mannitol, and respiratory equipment for the institution of hyperventilation).

Treatment

As with other syndromes discussed in this chapter, the sine qua non of HACE treatment is reversal of the underlying pathophysiology, via either rapid descent to lower altitude or use of some mechanical means (e.g., barometric chamber) to increase the patient's experienced barometric pressure (rarely a practical possibility) *(299,300)*. Climbers and skiers must monitor themselves and their companions for signs of altered alertness or mentation, ataxia, and increasing lethargy, and hasten descent if they occur. Patients with pulmonary edema should be intubated. Moderate levels of PEEP (up to 10 cm H_2O) and high but nontoxic FiO_2s (up to 0.60) should be utilized to reverse hypoxemia. Nifedipine 10 mg orally every 4 h may be beneficial to pulmonary physiology *(302)*, but has not been evaluated as an acute treatment in intubated patients. Dexamethasone 10 mg IV followed by 4 mg every 6 h is advocated as highly efficacious by those in the field *(299,300)*; we are skeptical, because formal published evaluations to date have been insufficient to conclusively establish the efficacy of steroids. It is clear that they are no substitute for return to higher barometric pressure *(303)*. Clinical wisdom is that earlier descent and treatment favor good outcome *(300)*.

Prophylaxis

In this as in every disease, an ounce of prevention is worth a pound of cure. Optimally, a traveler from altitudes near sea level should acclimate in areas near 2500 m for 2 d before ascending to peak areas. Acetazolamide taken prophylactically before travel, starting the day before departure from home altitudes, has been shown to be effective at reducing the incidence of AMS *(304,305)*; this has been taken as indicating a probable decrease in the risk for HACE, but without strong data. Nifedipine 20 mg orally every 8 h *(302)* or salmeterol 125 μg by metered-dose inhaler every 12 h *(306)* are of demonstrated efficacy in decreasing the risk of developing HAPE.

Lead Intoxication

Chronic exposure to lead produces well-known syndromes of neurobehavioral impairment in children and sensorimotor neuropathy in adults. With extremely high levels, a syndrome of impaired brain function referred to as lead encephalopathy ensues. Far more common in the pediatric than the adult population, the recognition of the adverse health and cognitive effects of lead have produced such successful attention to its eradication that this complication is uncommonly seen in the United States any longer. Nevertheless, cases do continue to occur *(307,308)*.

Clinical Manifestations

The symptoms of lead encephalopathy are nonspecific: headache; ataxia and dysarthria; abdominal pain, anorexia, nausea, and vomiting; fatigue and lethargy progressing to stupor and coma; and seizures *(307,309,310)*. Untreated, it is often fatal; in such cases, the brain is found to be diffusely

congested and edematous. Judging from the clinical phenomenology, it is likely that the pathophysiology is toxicity to cellular metabolism producing a diffuse cytotoxic edema. Susceptibility to this toxicity appears to be greater in the young *(311)*.

Diagnosis

The most crucial step in appropriate treatment of a patient with lead encephalopathy is diagnosis. The clinical presentation, given its nonspecific nature, is very frequently misattributed to systemic infection. The presence in the patient's history of any potential risk of lead exposure must raise the index of suspicion, as must the incidental detection of any of the laboratory abnormalities that commonly accompany longstanding toxicity (*see* below). The greatest risk factor is youth; children under the age of 6 yr are at particular risk of voluntary ingestion of lead-containing materials. Potential sources include peeling house paint (interior or exterior), water from inappropriately plumbed pipes, soil from around old houses or other painted structures, batteries, solder, fishing weights, folk medicines (azarcon and Greta from Mexico, Pay-loo-ah amongst Chinese and Hmong), cosmetics (surma, ceruse, and kohl, from Asia), and many other materials *(312,313)*. Parents of young children should be carefully interrogated for a history of pica *(307,308)*. Adults are typically exposed in industrial environments, such as smelting, soldering, battery manufacture, demolition and remodeling in old buildings, ships and bridges *(309)*, and the consumption of illegally distilled alcohol ("moonshine") *(314,315)*. Illegal alcohol represents a particularly insidious source, as it could be clinically tempting to attribute the symptoms and signs of lead toxicity to a combination of acute alcohol intoxication with coexistent effects of chronic alcohol abuse *(314)*.

In a few cases, there may be evidence on the clinical examination to suggest the diagnosis: wrist or foot drop may have developed if peripheral neuropathy is advanced, and visible bluish discoloration of the teeth at the gum line may be evident *(312,316)*. These features are much more frequently absent, however, especially in children *(316)*, and their absence should not be taken as evidence against lead toxicity.

Laboratory diagnosis is straightforward: demonstration of a severely elevated serum lead level—higher than 60 μg/dL, often in the hundreds in cases with encephalopathy *(307)*. Unfortunately, not all clinical laboratories have the capacity to run a lead level on an emergent basis, and other biomarkers may need to be used as supportive evidence while the definitive test is pending. The most specific of these is erythrocyte protoporphyrin, commonly elevated due to lead's interference with the heme synthesis pathway *(310)*. This biochemical disturbance produces the characteristic hematologic manifestation, of great clinical utility given the place of the complete blood cell count in standard laboratory evaluations: a normochromic, normocytic anemia. On microscopy, some erythrocytes may exhibit basophilic stippling. Serum uric acid may be elevated. At serum concentrations of lead sufficient to produce cerebral edema, there is often also an interstitial nephritis producing increased blood urea nitrogen and creatinine. Bands of density ("lead lines") may be seen on skeletal radiographs due to lead deposition in bone *(307,308,317)*. Most of these biochemical abnormalities require at least several weeks of biologic exposure to develop *(310)*; however, an acute exposure to a quantity of lead is more likely to produce encephalopathy if the patient already had an elevated lead level, and a search for evidence of preexisting lead toxicity may pay dividends if one is forced to wait for a lead level. In a patient without preexisting toxicity exposed to a catastrophic amount of lead, one may be left to depend on the clinical history and serum lead level alone. CSF examination in a patient with lead encephalopathy may reveal elevated protein and mild cellularity, usually monocytic, potentially misleading the clinician into a diagnosis of meningitis *(318)*.

Treatment

The sine qua non of optimal management is chelation therapy to emergently lower lead levels. Commonly used agents are calcium disodium edetate ($CaNa_2EDTA$), dimercaprol (BAL), and succimer (DMSA); D-penicillamine may also be used, although it is generally considered appropriate

only if the other agents are unavailable *(310,312)*. Recommended dosages depend on the source, and consultation with the pharmacy is advised. It is generally agreed that a combination of BAL and $CaNa_2EDTA$ is the first-line regimen, producing a rapid fall in serum lead level *(319)*. There is a report *(307)* of the safe use of EDTA, BAL, and DMSA concurrently in a 3-yr-old patient with a serum lead concentration of 550 mcg/dL.

The cerebral edema of lead encephalopathy must only be managed while the underlying toxin is removed. Fortunately for society, such cases are sufficiently rare today that no one has accrued any appreciable case series in the modern era of ICP management. Optimal management is therefore a matter of conjecture. Given that multiple-chelator regimens appear to return serum lead levels to less than 50 μg/dL within one and at the most 3 d after initiation of therapy, avoidance of the iatrogenic risks of ICP monitor placement is defensible *(307,319)*. Standard measures of positioning, ventilatory support, temperature control and cardiovascular and metabolic stabilization should be scrupulously applied; the judicious use of mannitol or barbiturates in those patients with severe encephalopathy are conceptually justifiable, but no data exist to guide their appropriate use. As an almost historical note, decompressive craniectomy has been tried in the past *(320,321)*, and although not subjected to a controlled trial, subsequent publications reported an increase in mortality *(322)*. Seizures complicating lead encephalopathy should be managed very aggressively, from the complete reversibility of the underlying pathophysiology. If seizures do not respond to aggressive doses of lorazepam (0.2 mg/kg), rapid progression to barbiturates or propofol might be considered preferable to waiting for the completion of a phenytoin load.

The majority of potential exposures to lead are by ingestion. In any patient with lead encephalopathy, therefore, a flat abdominal radiograph should be obtained to assess for radiopaque material in the gastrointestinal tract. Any material so detected represents a potential source of further absorption of lead, and should be evacuated to prevent further increases in the serum lead level. The effective use of whole bowel irrigation with polyethylene glycol solution has been reported *(323)*, and should be quite safe provided no contraindications to its use are present (bowel perforation or obstruction, ileus, uncontrolled gastrointestinal hemorrhage, uncontrollable vomiting, unsecured compromised airway, hemodynamic instability) *(324)*. The recommended regimen is 1500–2000 mL/h by nasogastric tube in adults (500 mL/h in children 9 mo–6 yr, 1000 mL/h in children 6–12 yr), with a drop to half-rate if emesis occurs; this should be continued until the rectal effluent is clear—generally anywhere from 3–12 h *(324)*.

Outcome

In the modern era of multiple-chelator regimens, even extraordinarily high lead levels are survivable *(307)*. Reports from before the establishment of combinations of chelators as the preferred treatment suggest a mortality rate of approx 30% among children comatose from lead poisoning *(322,325)*. Within a few years of these reports, series using EDTA and BAL in combination reported mortality rates of 0–5% in similar children *(317,319)*. With timely recognition and immediate institution of appropriate therapy, lead encephalopathy would appear to be an eminently survivable disease.

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