Recent Advances in CSF Physiology

Fred Plum, M.D.,* and Bo K. Siesjö, M.D.,†

The cerebrospinal fluid (CSF), sometimes regarded in the past as an uninteresting and fairly stagnant pool that passively fills the ventricles and cisterns of the central nervous system, has been the subject of intense investigation in recent years. The results indicate that CSF, apart from offering important mechanical cushioning to the brain, is in free communication with the organ's interstitial fluid (ISF) so that ISF plus CSF make up the extracellular fluid (ECF) of the brain. The circulation and composition of the CSF are probably indispensable to the narrow homeostasis that neurons require for their normal function. Furthermore, the fluid, with its continuous unidirectional net flow, appears to serve the brain as a major biological river, transporting humoral messages from one region to another and serving as an important route for the removal of a variety of waste products produced by cellular metabolism. The present review summarizes recent information on 1) production, absorption and ionic composition of CSF, and 2) regulation of the CSF pH, as well as the consequent importance of changes in CSF pH for the regulation of pulmonary ventilation and cerebral blood flow. For some of these topics the clinical implications of the physiologic data are discussed. Other recent reviews may be consulted for a more thorough account of specific aspects of the subject.

Production and Absorption of CSF

It has been the conventional view since Weed, Dandy, Flexner, and Cushing made their now-classic observations during the early part of this century that a major part of the CSF is formed in the choroid plexuses of the cerebral ventricles and reabsorbed from the surface of the brain through pachionian granulations of the large dural sinuses. Recent research has largely confirmed this concept and has quantified the dynamics of the CSF system. Much of our recent understanding of CSF dynamics comes from the quantitative exploitation by Pappenheimer, his colleagues, and others of the technique of ventriculocisternal (V-C) perfusion. In this method an artificial CSF is pumped into a cannula inserted in the lateral ventricle of an animal (or man), and the outflowing fluid is collected at a downstream site, usually the cisterna magna. If one includes in the perfusion a metabolically inert substance such as inulin that does not diffuse out of the ventricular fluid, the dilution of the inulin concentration as it leaves the ventricles reflects the bulk rate of CSF formation. We obtain

\[
V_{\text{CSF}} = \frac{C_{\text{in}} - C_{\text{out}}}{C_{\text{out}}} \cdot V_{\text{in}}
\]

where \(V_{\text{CSF}}\) and \(V_{\text{in}}\) are the volumes of formed (native) and infused (artificial) CSF, respectively, and \(C_{\text{in}}\) and \(C_{\text{out}}\) are the inulin concentrations in the infused and recovered CSF, respectively. The rate of CSF absorption may also be determined if one measures the volume of recovered fluid. The absorption (clearance) is then calculated as

\[
V = \frac{V_{\text{in}} \cdot C_{\text{in}} - V_{\text{out}} \cdot C_{\text{out}}}{C_{\text{out}}}
\]
RATE OF PRODUCTION

Rates of CSF formation have been measured in rats, rabbits, cats, dogs, and goats, and approximate 2, 10, 20, 50, and 150 \( \mu \text{L/min} \), respectively.\(^\text{37,46}\) In children with intraventricular canulae in place, the rate of production has been determined to be about 350 \( \mu \text{L/min} \).\(^\text{49}\) Thus, in all these species, an amount of fluid equal to the total CSF volume is produced in about 4 hours. The rate of CSF production has been found to remain constant between CSF pressures of -5 and +20 mm Hg. An increased rate of production does not seem to occur under physiologic conditions; experimentally, increased production has been reported to occur after administration of the diuretic, spirolactone,\(^\text{55}\) and after v-c perfusion of fluids with a low (10^{-16} \text{ mole/L}) concentration of ouabain.\(^\text{59}\) Under pathologic conditions in man, increased CSF production accompanies some papillomas of the choroid plexus.\(^\text{56}\) Also, Cutler \textit{et al.}\(^\text{41}\) have recently documented a CSF production rate of 1.7 \( \mu \text{L/min} \) (about four times the normal rate) in a child with hydrocephalus, another demonstration of the importance of such mechanisms in disease.

A decreased production of CSF is obtained in hypothermia,\(^\text{46}\) in respiratory and metabolic alkalosis,\(^\text{128}\) and after administration of a variety of drugs, including acetazolamide, furosemide, ouabain, spirolactone, amiloride, amphotericin, and vasopressin.\(^\text{47}\) Acetazolamide and furosemide each reduce the rate of secretion by about 50 per cent, and the two drugs together may possibly have an additive effect.\(^\text{10}\) It has also been reported that the rate of secretion decreases in experimental hydrocephalus induced by intracisternal administration of kaolin, an effect attributed to denudement and destruction of choroid plexus cells, and not to the increased pressure \textit{per se}.\(^\text{28}\) Unfortunately, none of the pharmacologic measures found to reduce secretion has been demonstrated to do this chronically, which limits their usefulness in clinical conditions. The standard anesthetic agents have not been studied to determine whether they influence CSF production or absorption.

MECHANISMS OF PRODUCTION

The secretion of the CSF is an energy-requiring process, and the fluid differs substantially from a simple ultrafiltrate of plasma. CSF production occurs even if the ventriculo-cisternal system is perfused with hypotonic fluids, indicating that water transport can occur against a chemical gradient.\(^\text{14,179}\) Furthermore, chemical analyses of newly formed CSF at the surface of the plexus show that the fluid formed differs significantly in composition from that of an ultrafiltrate.\(^\text{3,120,153}\) The effect of drugs upon the rate of CSF formation indicates that the fluid is formed by molecular mechanisms that to a considerable extent are catalyzed by carbonic anhydrase and apparently involve the operation of an ouabain-sensitive sodium-potassium-activated ATPase.\(^\text{105,172,153}\) These properties are similar to those of secretions occurring elsewhere in the body (stomach, pancreas). It has been suggested, however, that choroidal blood flow may impose an upper limit of the rate of CSF secretion,\(^\text{7}\) and it remains a possibility that at least some of the factors that affect CSF secretion do so by altering choroidal blood flow.\(^\text{37}\)

SITES OF PRODUCTION

Cushing, Dandy and many subsequent neurosurgeons directly viewed watery fluid coming from the ventricular choroid plexus in patients at operation and, as mentioned above, Rougemont \textit{et al.},\(^\text{121}\) using painstaking techniques, were able to collect from the surface of the plexus fluid that represented the primary CSF secretion. Using a technique that measures the loss of fluid from the blood when it passes the choroid plexus tissue, Welch\(^\text{176}\) concluded that the plexus generates most of the fluid that flows through the ventricles. However, even the pioneers in the field recognized that not all of the CSF comes from the plexus, and this has been confirmed by experiments demonstrating fluid formation by the aqueductal ependyma\(^\text{149}\) and perhaps even in the cerebral subarachnoid space,\(^\text{139}\) although not within the spinal subarachnoid space.\(^\text{172}\) Pollay and Curl\(^\text{139}\) estimated that non-choroidal sources could generate as much as 30 per cent of the
ventricular CSF, and later results indicate that even this figure may underestimate the potential flow from such sources in pathologic conditions. Not all authorities accept an extra-choroidal source of the CSF, but what evidence exists on the subject is compatible with there being a slow flow of fluid along the interstitial channels of the brain, which may aid in the removal of substances from the vicinity of actively metabolizing cells. This "lymphatic" function of the circulating CSF, the "sink effect" of Davson, may provide an important route for the removal of many high-molecular-weight substances that cannot leave the tissue by crossing the capillary endothelium (proteins, transmitter molecules, etc.).

SITE AND MECHANISM OF ABSORPTION

Modern studies largely support the classic view that the CSF formed within the ventricles of the brain exits from the fourth ventricle and washes forward over the surface convexities of the hemispheres, to be reabsorbed in bulk through the arachnoid villi that lie in Pacchionian granulations and at dural reflection sites of the cranial and spinal nerves. It was the traditional view established by Weed that the CSF escapes from the arachnoid villi into the blood by membranous filtration. However, Welch and Friedman concluded from their own morphologic and in-vitro perfusion studies that the arachnoid villi contain tubular, pressure-sensitive, unidirectional valves capable of passing particles perhaps 4–12 μ in diameter from the CSF into the large venous sinuses. By virtue of their unidirectional nature, these valves would prevent regurgitation of blood into the CSF when the pressure gradient is from venous blood to CSF. Such a valvular system would go far in explaining how the CSF constantly rids itself of protein, cellular debris, erythrocytes, and products of metabolism, and the appealing nature of the concept led to its quick acceptance by physiologists. Initially, investigators using electron microscopy failed to find any evidence of "valves" in the arachnoid villi that interrupt the tight junctions of the dural sinus epithelium. However, more recent work in which morphologic studies were combined with special antemortem preparation of experimental animals appears to indicate the presence of several appropriate escape routes from CSF to sinus blood via the arachnoid granulations. Alsken and Lovings showed pinocytosis in the endothelial cells of the arachnoid villi of animals in which cerebrospinal fluid pressures were kept high before sacrifice and histologic fixation, and Gomez et al. found that the amount of such pinocytosis is proportional to the pressure. Furthermore, under conditions of physiologically raised CSF pressures, the intercellular spaces in the arachnoid granulations widened, as did spaces between the endothelial cells at the tips of the granulations, establishing visibly in some instances a direct passage between the subendothelial space and the lumen of the sinus. Depending as it did on subarachnoid pressure for its patency, the system provided unidirectional access, from subarachnoid space to blood, of particles that could be as large as intact erythrocytes.

Physiologic studies seem to establish that the factor determining CSF absorption is the hydrostatic pressure difference between CSF and sinus blood, and not any difference in osmotic pressure. Heisey et al. established some time ago that the rate of absorption of CSF normally varies directly with the CSF pressure, between zero at pressures of +5 mm Hg and maximal, with a rate of about three times the formation rate, at pressures of 15–20 mm Hg.

RELATIONSHIP BETWEEN CSF AND CEREBRAL INTERSTITIAL FLUID

Modern studies have confirmed the classic observation originally made many years ago with vital dyes that membranes separating blood from brain tissue and the CSF differ in their permeability characteristics from those of other capillary areas in the body. In general, the blood–brain and the blood–CSF barriers have the permeability characteristics of cell membranes, rather than systemic capillary endothelium. Lipid-soluble molecules such as anesthetic gases readily penetrate the brain and CSF barriers, but large water-soluble molecules, especially of a polar nature, have restricted passage. Fur-
thermore some substances cross the membrane in concentrations indicative of an active transport mechanism. The site of the blood–brain barrier has been disputed, some investigators favoring the astrocyte, others believing that the limiting and transfer functions lie in the capillary endothelium. Most recent evidence favors the cerebral capillary endothelium as comprising at least a large proportion of barrier functions.

In the endothelium of most regions of the brain each cell is continuously welded to its neighbors by tight junctions which are visible ultramicroscopically and which give to the endothelium the anatomic effect of being a continuous membrane. Ultrastructural studies utilizing electron-dense peroxidases, which range in molecular weight from 48,000 to about 4,000,22-26 have shown that when injected into the systemic circulation, none of the peroxidase material penetrates the endothelium of the brain, except in specialized small regions, mentioned below. On the other hand, when peroxidase is injected into the cerebral ventricles it circulates along the usual CSF passage, and slowly trickles between the ependymal cells of the ventricles to find its way into all reaches of the intercellular space of the brain, eventually penetrating to the inner or extravascular side of the tight junctions of the capillary endothelium.

Despite the anatomic evidence for a blood–brain barrier at the endothelial wall, other mechanisms in the brain must also serve similar functions. This is illustrated by the fact that certain capillaries “leak,” permitting large molecules to diffuse from blood to brain at several restricted sites, including the choroid plexus, area postrema, infundibular area, and pineal region. Anatomic studies show that at the plexus the choroidal endothelium prevents the further passage of peroxidase,21 but in the other areas, diffusion of macromolecules remains limited to a narrow zone around the permeable area without visible structural differences to explain what mechanism effects the limitation. The functional explanation of these restricted zones of increased permeability is unknown, although their anatomic positions would make them ideal sites for chemoreceptor functions.

Recent studies indicate that the blood–brain barrier can be opened reversibly by several mechanisms, including injection into the carotid artery of highly osmotic salts,16 the presence of acute hypertension,21 or seizures.21 Inhalation of 7 per cent carbon dioxide,28 and injection of several radiographic dyes.18 The functional importance of such temporary changes in barrier mechanisms, and especially their relation to cerebral vascular autoregulation, is presently receiving considerable study.

The composition of CSF is the complex result of diffusion or secretion across the choroid plexus epithelium and of secondary exchanges between the ISF and the brain parenchyma. Some substances, such as highly permeable lipid-soluble molecules, equilibrate more rapidly with the tissue than with the CSF. For such substances the CSF acts as a “sink,” delaying equilibration with the tissue. This “sink” action also applies to slowly equilibrating substances that are mainly confined to the extracellular fluid (inulin, mannitol, sulfate, iodide). When these substances are introduced and maintained at constant concentration in the blood, their brain-tissue concentrations are only a fraction of the plasma concentrations; such findings originally led to the erroneous conclusion that the volume of the extracellular fluid in the brain is only 2–4 per cent of the tissue weight. Subsequent studies, in which the tracer material was introduced from the CSF side (v-c perfusion), have indicated an ECF volume of approximately 20 per cent of the tissue weight.51,127,146,161,182

The CSF concentrations of some substances are regulated by homoeostatic mechanisms that maintain constant or near-constant concentrations, in spite of wide fluctuations in the corresponding plasma concentrations. Notable among these substances are the physiologically active ions, K+, H+, Mg++, and Ca++.1,5,21,27,45,161,251 To a large extent, the constant CSF concentrations of such ions seem to depend on secondary exchanges between freshly formed CSF and cerebral interstitial fluid, the composition of which is partly determined by ion transport across the blood–brain barrier.17 In other words, active transport regulation of the CSF concentrations of many ions occurs both across the plexus epithelium and across the capillary endothelium. Whether anesthetics affect these systems appears not to have been tested.
CLINICAL IMPLICATIONS OF CSF DYNAMICS

The volume of the CSF in the adult averages about 140–170 ml, equivalent to about 10 per cent of the intracranial volume. The fluid buoyed about 97 per cent of the weight of the slightly denser brain, 37 lubricating it and substantially protecting it against trauma during cranial movement. Clinical evidence suggests that the buoyancy prevents traction and displacement of the brain on its pain-sensitive intracranial attachments during changes in position of the head. The fluid also may serve to transmit the pulses of the blood pressure out of the cranial cavity and into the more elastic spinal canal; the papilledema that sometimes accompanies neoplasms of the upper spinal cord and the hydrocephalus that accompanies cerebral adhesive arachnoiditis (communicating hydrocephalus) could result at least partly from the loss of this cushioning effect. The importance of the buoyancy is illustrated by the severe pain associated with partial replacement of CSF by air after pneumoencephalography, and by the orthostatic headache that may follow lumbar puncture. In these instances the finding of spinal dural leaks during laminec 32 tomy as well as lumbar leaks detected after isotope myelography, 39 suggests that traumatic leakage exceeds the rate of CSF formation. Since post-lumbar-puncture leakage may be long-lasting and incapacitating, the findings emphasize the need for using small needles and delicate techniques when performing spinal puncture.

Under normal conditions, the intracranial CSF pressure is determined by a balance between the rates of secretion and absorption of CSF. Superimposed upon the resulting CSF pressure are rapid fluctuations that result from the pulse pressure, and slower changes that accompany variations in intracranial blood volume. Such variations, which may occur in hypocapnia and hypercapnia, are usually compensated for by decreased or increased absorption of CSF in these conditions. The increased CSF pressure that follows administration of volatile anesthetics such as halothane, trichloroethylene, and methoxyflurane 32,34,111 is probably secondary to directly-produced vasodilatation and a resulting increase in cerebral blood volume. Even when the anesthetic is continued, the pressure tends to normalize within 10–20 minutes, mainly as a result of increased CSF absorption, although the relative vasodilatation also subsides. Hyperventilation of the patients before the anesthetics are administered can modify the increase in pressure. 2,52

In obstructive hydrocephalus impaired absorption of CSF leads to increased CSF pressures and dilatation of the ventricles, since CSF production continues even if the pressure increases. Communicating hydrocephalus, in which the obstruction to CSF flow lies outside the ventricular system, has long been recognized as a problem in infants and young children, and recent years have seen its recognition as a problem in adults as well. The condition varies considerably in its aetenueness and severity. Rapidly developing cases, such as occur shortly following subarachnoid bleeding, or with the granulomatous meningiites of cryptococcosis, tuberculosis, or lymphoma, are usually characterized by fairly florid clinical changes (delirium, confusion and stupor) and high CSF pressures (>150 mm CSF). Subacute or chronic obstruction to CSF flow produces in adults a more subtle disorder, with apathy, dementia and corticospinal tract dysfunction. The condition sometimes can be clinically difficult to separate from degenerative diseases causing dementia, such as Alzheimer's disease, or multifocal cerebral infarction. Adding to the diagnostic difficulty is the fact that CSF pressure in adult hydrocephalus may not always exceed the conventionally regarded upper limit of normal of about 150–160 mm CSF.103,113 As a result, communicating hydrocephalus in adults sometimes produces a normal-pressure hydrocephalus” (NPH). The observation that patients with this condition sometimes improve after shunting of the cerebral ventricles 1 has stimulated a number of efforts to identify proper candidates for operation by clinical or laboratory studies. Clinically, most patients with NPH and dementia are apa-
thetic, slow in thought and motion, have increased muscle resistance to passive motion, extensor plantar responses, a broad-based gait and, often, urinary incontinence. The absence of increased intracranial pressure and the fact that pneumoecephalograms sometimes fail to predict patients who will improve from shunting have prompted the use of other tests of spinal fluid absorption to aid in diagnosis. These include isotope encephalography and the measurement of CSF pressure during subarachnoid perfusion (Katzman test). Some authors have also employed the recording of intracranial pressures over a period of several hours in an effort to detect abnormal pressure waves ("plateau" waves of increased pressure). 14

Isotope encephalography is a procedure developed by di Chiro 31, 52 in an effort to outline the circulation of the CSF by injecting radioactively labeled albumin into the subarachnoid space. When injected into the lumbar area, the isotope passes cranially, into the cisterna magna and then over the surface of the brain to enter the blood, mainly at the sagittal sinus. In a majority of normal patients, most of the isotope leaves the head after 24 hours, and very little enters the ventricular system. Early experiences suggested that, in contrast to the normal situation, patients with severe communicating hydrocephalus have dense isotope filling of the cerebral ventricles, which may last as long as 72 hours, with little or no isotope entering the subarachnoid space over the cerebral convexities. 31, 57 However, further clinical experience has been disappointing, finding the isotope study to be inconsistent in diagnosing the cause of hydrocephalus, at least as judged by the effects of subsequent ventricular shunting. 34, 71

The manometric infusion test, developed by Katzman, 20, 24 is based on the knowledge that the rate of CSF formation normally is about 0.35 ml/min and that the rate of absorption can reach at least three times the rate of formation if the CSF pressure rises. The test consists of infusing physiologic saline solution at a rate of 0.76 ml/min into the lumbar subarachnoid space and repeatedly measuring the ensuing pressures. Abnormal absorption is characterized either by higher-than-normal steady-state pressures or by a progressive rise in pressure to more than 35 mm Hg during the infusion. It remains for further clinical investigations to demonstrate exactly which pathologic intracranial processes underlie abnormal responses of this kind, although, even in Katzman's hands, 24 the test has provided inconsistent accuracy in diagnosis. It has been a disappointing development that clinical studies of adult hydrocephalus indicate that unless the specific cause of communicating hydrocephalus is known, no single test or even combination of tests seems able to predict whether shunting will have a favorable effect. 31, 106

To a certain extent, variations in the intracranial blood or CSF compartments reciprocally compensate each other. It has already been mentioned that as intracranial pressure rises the absorption of CSF proportionately increases to as much as three times its resting level. With space-occupying processes such as tumors, hematomas, or cerebral edema, however, the volume capacity of the intracranial cavity declines, limiting the system's elasticity. This principle explains why at low CSF pressures a given absolute increase in volume may be followed by only a small rise in pressure, whereas at increased pressures the same volumetric increase produces a marked increase in pressure. As a result small increases in the volume of the brain, the blood compartment, or the mass can precipitate dangerous increases in pressure in patients with mass lesions and increased intracranial pressures. In such patients, cerebral vasodilatation caused by administration of anesthetics such as halothane, or increases in the CO₂ tension, may be deleterious. 89 Small increases in intracranial blood volume in patients with increased intracranial pressure are reportedly responsible for transient "plateau waves," which may reach pressures of 100–140 mm Hg. 106 The occasionally beneficial effect of hyperventilation on patients with elevated CSF pressures 106 probably acts via a reduction in intracranial blood volume, the result of arteriolar constriction.

Although recent advances in CSF physiology have improved our understanding of
pathologic changes in CSF dynamics, and also stimulated the development of diagnostic procedures, they thus far offer little help in therapy. Thus, neither lowered blood CO₂ tensions nor drugs can completely turn off the flow of cerebrospinal fluid, and drugs such as acetazolamide, which cause drastic reduction in CSF formation under acute conditions, become ineffective after a few days of administration in most hydrocephalic patients.109 These facts imply that the formation of CSF may be indispensable to the brain, and they underscore why disease conditions that impede the normal egress of CSF are so hard to treat with nonsurgical measures. The physiologic data, which indicate that a substantial amount of the CSF is formed from extra-choroidal sites, provide an explanation for the fact that among the surgical measures used to normalize CSF pressure, plexectomy is inefficient.119

**Clinical Implications of Chemical Regulation of CSF Content**

The physiologic and chemical mechanisms that maintain chemical homeostasis of the extracellular fluids of the brain are so effective that the system usually goes awry only in the presence of severe and relatively acute illnesses, at which time one is hard put to separate symptoms that could be caused by abnormal CSF regulation from those caused by the primary disease itself. It is easier, however, to identify clinical disorders that may be caused by changes in the osmolality of the cerebral fluids.

The low permeability to electrolytes and other osmotically active particles of the blood-brain and the blood-CSF barriers makes the brain sensitive to hypo-osmolality or to water intoxication. During water loading the peripheral tissues become dilute, but particles leave the brain less rapidly. The resulting hyperosmolality of the brain’s ECF is quickly diluted by freely permeable water.12,16 According to Fishman,60 cellular volume is relatively preserved under these circumstances but the cells lose potassium. Whatever the specific mechanism, when plasma osmolality decreases rapidly (as during the sudden ingestion of a large volume of water or in diseases that induce inappropriately abundant antidiuretic hormone secretion), delirium, motor twitching or convulsions often result.

The converse condition of serum hyperosmolality also affects the brain, and sometimes is employed therapeutically to treat abnormal swelling of the brain with agents such as urea, mannitol, glucose, or glycerol. All of these substances increase the osmolality of the blood and, at least immediately, tend to pull water from the brain, an effect that can either shrink the abnormal area or reduce its mass effect by dehydrating the normal brain. How long the effect lasts depends on the molecular size of the osmotic agent used (urea slowly diffuses into brain over a few hours) and whether, like glucose, the agent is metabolized or transferred into brain. Urea poses special problems. Its use to treat intracranial conditions sometimes is followed by a "rebound" effect, with increased intracranial pressure and clinical deterioration. This occurs when plasma concentrations begin to fall below the concentration that has diffused into the brain, resulting in water movement back into brain to balance the osmolality. A similar sequence is sometimes believed to operate during hemodialysis for renal failure. The dialysis abruptly lowers blood urea concentration, and transient delirium can be associated with water diffusion back into the now relatively hypertonic brain.61 Employing a slower rate of dialysis or raising the serum osmolality with a nondiffusible sugar during hemodialysis prevents the problem.62

**Regulation of CSF pH**

Changes in the pH of cerebral extracellular fluids exert important physiologic effects, and thus hydrogen ion concentration of the fluid normally is maintained within extremely narrow limits. It has been proposed that the pH of cerebrospinal fluid uniquely regulates pulmonary ventilation.52-59,121 and it appears that ECF pH profoundly affects cerebral blood flow.12,52,67,122 These two influences undoubtedly play an important homeostatic role in maintaining the pH of cerebral extra- and
intracellular fluids. The CSF pH also appears to be regulated by other physiologic systems, and in recent years many efforts have been made to identify these mechanisms, and evaluate their quantitative importance.

In this section we discuss recent studies bearing on the regulation of CSF pH. In order to facilitate discussion of specific results, we first briefly summarize the fundamental acid-base characteristics and the acid-base composition of CSF. It seems warranted also to define from the beginning some of the salient features of CSF acid-base regulation. These are: 1) In steady-state conditions the $H^+$ and $HCO_3^-$ concentrations of bulk CSF can be assumed to reflect the corresponding concentrations in cerebral ICF. 2) $H^+$ and $HCO_3^-$ ions are not in electrochemical equilibrium between plasma and CSF, indicating that one or several mechanisms continuously acidify the cerebral extracellular phase. 3) The CSF pH is remarkably well regulated in some chronic plasma acid-base disturbances, notably the nonrespiratory ("metabolic") ones. This very fact indicates that specific regulatory mechanisms maintain CSF pH within a very narrow normal range, and it has been widely assumed that active transport mechanisms are responsible for the pH homeostasis. However, as the discussion will show, the evidence for this is incomplete and inferential, and one must consider alternative mechanisms.

**ACID–BASE CHARACTERISTICS OF CSF**

The CSF (and cerebral extracellular fluid in general) contains only negligible concentrations of buffer anions other than $HCO_3^-$. This has two consequences. First, there is a mole-to-mole relationship between added acid or base ($\Delta$ buffer base) and the ensuing change in $HCO_3^-$ concentration. Second, if CSF does not exchange ions with the surroundings (as is the case when CSF is placed in a tonometer), variations in $P_{CO_2}$ do not cause measurable changes in the $HCO_3^-$ concentration of the fluid. It follows from the latter that variations in CSF $[HCO_3^-]$ in vivo must be due to exchanges of $HCO_3^-$ (or $H^+$) with either tissue or blood.

The acid–base composition of CSF is given by the equation:

$$[BB] = [T_{CO_2} - P_{CO_2} \cdot S]$$

$$= \frac{P_{CO_2} \cdot S \cdot K'_v}{[H^+]} \left( 1 + \frac{2 \cdot K'_v}{[H^+]^2} \right) \quad (3)$$

In this equation $[BB]$ is the buffer base concentration, $T_{CO_2}$ is the total $CO_2$ content, $S$ the solubility factor, and $K'_v$ and $K'_v$ the first and second apparent ionization constants of $H_2CO_3$. In most situations the pH of CSF is sufficiently acid to permit neglect of the $CO_3^-$ concentration, and we may write the logarithmic form of the equation as

$$pH = pK'_v' + \log \frac{T_{CO_2} - P_{CO_2} \cdot S}{P_{CO_2} \cdot S} \quad (4)$$

where $T_{CO_2} - P_{CO_2} \cdot S$ then equals the $HCO_3^-$ concentration and one has the conventional equation

$$pH = pK'_v' + \frac{[HCO_3^-]}{P_{CO_2} \cdot S} \quad (5)$$

At 37°C, $pK'_v$ is 6.131 and $S$ is 0.0318 mmol/l · mm Hg. It should be remembered that $HCO_3^-$ cannot be measured directly, but must be calculated from equation 4, and that $pK'_v'$ varies with temperature. For accurate calculations these latter variations should be taken into account.\(^{123}\)

The low capacity of CSF to buffer changes to $P_{CO_2}$ contributes to the well-documented difficulty of measuring CSF pH accurately. Thus, if anaerobic conditions are not strictly maintained during and after sampling, or if air bubbles are allowed to remain in the syringe when withdrawing the sample, one obtains spurious results. It has been recommended that the $pH$ electrodes should be repeatedly flushed with CSF without intermediate rinsing,\(^{58,59}\) and some authors go so far as to refrain altogether from direct $pH$ measurements of CSF and prefer to calculate $pH$ from $[HCO_3^-]$ and cerebral venous blood $P_{CO_2}$ measurements.\(^{58}\) It should be mentioned that reproducible measurements require that the patient be in a respiratory steady state at the time of sampling, and some investigators advise monitoring the alveolar (or arterial) $CO_2$ tension to assure stability before sampling.
ACID–BASE COMPOSITION OF CSF

Acid–base values in CSF have been measured by a number of groups, especially during the last ten years. The results of these measurements in normal subjects at sea level are quite consistent. However, in order to exemplify the acid–base relations between arterial blood and either lumbar CSF or cisternal CSF, we have chosen to supplement our own data with the values published by authors who have used their methods to derive the constants of equation 3 also (table 1). The data show that both lumbar CSF and cisternal CSF have higher CO₂ tensions and lower pH’s than arterial plasma.

It was originally reported by Bradley and Semple that the acid–base compositions of lumbar CSF and cisternal CSF were the same. However, van Heijst et al. studied a larger series of relatively normal patients and found that although the bicarbonate concentrations were the same in the two fluids, the lumbar CSF had a slightly higher P<sub>CO₂</sub>, and thereby a significantly lower pH. These authors used meticulous techniques for measuring the acid–base variates, and their absolute values for cisternal CSF are similar to those of Schwab.

Plum and Price also studied lumbar–cisternal acid–base values in a large number of hospital patients, and found among relatively normal subjects in the steady state differences between the two fluids that were almost identical to the van Heijst findings. Lumbar CSF pH was more acid than cisternal CSF pH due to a higher P<sub>CO₂</sub>, but the fluids contained equal bicarbonate concentrations. Among acutely ill patients considerably wider differences between pH’s in the two fluids were observed (fig. 1), even when systemic acid–base balance appeared to be relatively stable. In most, but not all, instances where there were discrepancies, the cisternal CSF acid–base values were closer than the lumbar CSF values to the accepted normal range. The findings emphasize that in acutely ill patients analyses of lumbar CSF provide unreliable and sometimes even misleading information about the acid–base status of cerebral extracellular fluid. This is particularly likely to be the case in conditions such as meningitis, carcinomatosis, or subarachnoid hemorrhage, where local glycolysis in the lumbar sac can raise the regional lactate concentrations and thereby reduce the pH of lumbar fluid.

There is presently no agreement as to the precise relationship between the CO₂ tensions in arterial blood, cerebral venous blood, and CSF. Lambertsen concluded from theoretical considerations that the CSF CO₂ tension should be close to that of cerebral venous blood, and Bradley and Semple confirmed this relationship in a few human subjects. Studies of lumbar CSF have shown that its CO₂ tension exceeds the P<sub>CO₂</sub> of arterial blood by about 10 mm Hg, and since the arteriovenous P<sub>CO₂</sub> difference in the brain is of the same magnitude, this seemed to confirm the equality of CSF and cerebral venous blood CO₂ tensions. In spite of all these results, however, there are reasons to question the validity of the conclusions. Thus, calculations using a simplified diffusion model predict that the mean tissue CO₂ tension (P<sub>CO₂</sub>), should be about 1 mm Hg above the arithmetic mean of the

Table 1. Acid–Base Data in Lumbar (L) and Cisternal (C) CSF of Human Control Subjects

<table>
<thead>
<tr>
<th>Number</th>
<th>Source</th>
<th>Arterial Blood</th>
<th>CSF</th>
<th>Difference</th>
<th>Arterial Blood</th>
<th>CSF</th>
<th>Difference</th>
<th>Arterial Blood</th>
<th>CSF</th>
<th>Difference</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>L</td>
<td>39.5</td>
<td>50.2</td>
<td>-10.7</td>
<td>24.8</td>
<td>25.1</td>
<td>-0.3</td>
<td>7.409</td>
<td>7.326</td>
<td>-0.083</td>
<td>Mitchell et al.</td>
</tr>
<tr>
<td>13</td>
<td>L</td>
<td>40.5</td>
<td>49.1</td>
<td>+ 8.6</td>
<td>24.3</td>
<td>24.9</td>
<td>+ 0.6</td>
<td>7.397</td>
<td>7.325</td>
<td>-0.072</td>
<td>van Heijst et al.</td>
</tr>
<tr>
<td>15</td>
<td>C</td>
<td>37.5</td>
<td>45.2</td>
<td>+ 7.7</td>
<td>24.9</td>
<td>23.6</td>
<td>-1.3</td>
<td>7.424</td>
<td>7.349</td>
<td>-0.075</td>
<td>Schwab</td>
</tr>
<tr>
<td>13</td>
<td>C</td>
<td>40.5</td>
<td>46.5</td>
<td>+ 6.0</td>
<td>24.3</td>
<td>24.9</td>
<td>+ 0.6</td>
<td>7.397</td>
<td>7.346</td>
<td>-0.051</td>
<td>van Heijst et al.</td>
</tr>
<tr>
<td>6</td>
<td>C</td>
<td>38.1</td>
<td>42.9</td>
<td>+ 4.8</td>
<td>24.7</td>
<td>22.1</td>
<td>-2.6</td>
<td>7.428</td>
<td>7.328</td>
<td>-0.100</td>
<td>Plum, Price</td>
</tr>
<tr>
<td>6</td>
<td>L</td>
<td>38.1</td>
<td>43.8</td>
<td>+ 5.7</td>
<td>24.7</td>
<td>21.5</td>
<td>-3.2</td>
<td>7.428</td>
<td>7.307</td>
<td>-0.121</td>
<td>Plum, Price</td>
</tr>
</tbody>
</table>
CO₂ tensions of arterial and cerebral venous blood, and therefore significantly lower than the cerebral venous blood CO₂ tension. In actual experiments, measurement of the tissue CO₂ tension can be approached either by using a tissue CO₂ electrode, or by using the cisternal CSF as a tonometer for the tissue. When such measurements have been performed in rats, cats and dogs, they have confirmed the theoretical predictions in showing that tissue CO₂ tension is about 1 mm Hg higher than mean capillary CO₂ tension. Earlier meticulous measurements of CO₂ tension in the cisternal CSF in man tended to support the findings in animal experiments, but left the question incompletely resolved, since they did not include observations on the jugular venous blood. However, Plum and Price directly measured PCO₂ in the arterial and jugular venous blood as well as the cisternal and lumbar spinal fluid in 18 acutely and subacutely ill patients (table 2). As can be seen, PCO₂ was lower in cisternal fluid (P < 0.001) than in either jugular venous blood or lumbar CSF, and corresponded closely to the prediction made from the above-mentioned simplified diffusion model,confirming the results of animal experiments.

Recently, Davies et al. developed an interesting hypothesis regarding acid-base changes at the capillary surfaces. The hypothesis predicts that the relationship between CO₂ tension in CSF on one hand, and CO₂ tensions in arterial and cerebral venous blood on the other, should vary with blood pH. The experimental results presented in support of the hypothesis are at variance with other results, including our own specific attempt to test the theory, and further evidence is needed if one is to accept Davies' hypothesis. Until such evidence is at hand we conclude that most results indicate that the CO₂ tension of cisternal CSF is not equal to the cerebral venous CO₂ tension. It must then also be emphasized that lumbar CSF does not truly reflect the acid-base composition of cerebral extracellular fluids and that interferes from measurements of lumbar fluid, particularly in unsteady states, must be drawn with caution.

As remarked previously, the cerebral ECF consists of several entities, including the primary CSF secretion, the bulk fluid CSF, and the ISF. There is evidence that the primary CSF secretion at the choroid plexus has a higher HCO₃⁻ concentration than has bulk CSF. This means that the CSF after its formation is subjected to secondary acidification, either by means of transcapillary transport of H⁺ from plasma to CSF, or by an outflux of acid from the tissue cells (see below). In the steady state, the H⁺ and HCO₃⁻ concentrations of bulk CSF
<table>
<thead>
<tr>
<th>Number</th>
<th>Arterial Blood</th>
<th>Jugular Venous Blood</th>
<th>CSF, Cisternal</th>
<th>CSF, Lumbar</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>30.6 ± 2.4</td>
<td>38.4 ± 2.4</td>
<td>35.1 ± 2.2</td>
<td>38.5 ± 2.3</td>
</tr>
</tbody>
</table>

* The difference between values for CSF and either jugular venous blood or lumbar spinal fluid is highly significant ($P < 0.001$).

cisternal) have been shown to be equal to the corresponding concentrations of true interstitial fluid. Thus, Fencl et al. perfused the CSF system of the goat with an artificial CSF and found that bicarbonate was neither lost from nor accumulated in the perfusion fluid when its \( \text{HCO}_3^- \) concentration was equal to that of the native (bulk) CSF in the given acid–base situation. In any nonsteady-state situation, however, large differences in acid–base composition may occur, not only between bulk CSF and interstitial fluid but also between cisternal CSF and lumbar CSF. This explains why it can be difficult to predict the acid–base composition of cerebral extracellular fluid from measurements of bulk CSF, especially from the lumbar region. The acid–base changes of bulk CSF are not in themselves of physiologic interest, but they gain their importance by reflecting true extracellular changes. For this reason we deal mainly with steady-state situations in the discussion to follow.

### Acid–Base Composition of Blood and CSF

The data of table 1 do not give a fair or complete account of the acid–base relations between CSF and plasma. The relevant comparison is between the \( \text{H}^+ \) and \( \text{HCO}_3^- \) concentrations in cisternal CSF and mean capillary (cerebral) plasma. By assuming that the mean capillary plasma \( \text{CO}_2 \) tension and the mean capillary plasma \( \text{HCO}_3^- \) concentration are the arithmetic means of the corresponding arterial and cerebral venous plasma values, and by calculating the \( \text{HCO}_3^- \) concentration per kg of plasma water, we arrive at the acid–base relations depicted in table 3. According to this calculation the \( \text{HCO}_3^- \) concentration in CSF is about 2.5 mEq/kg lower than that in plasma water, and there is a pH difference of about 0.02 units. However, the actual deviation from a true passive distribution is obtained only when one considers also the electrical d.c. potential between CSF and blood. In rats, goats, dogs, and man, the CSF is positive to plasma by about +4 mV at an arterial plasma pH of 7.40 and plasma \( \text{HCO}_3^- \) of 24 mEq/l. At this plasma pH and difference between CSF and plasma potentials a passive distribution of \( \text{H}^+ \) and \( \text{HCO}_3^- \), as calculated from the Nernst equation, would require a CSF pH of about 7.46 and a CSF \( \text{HCO}_3^- \) concentration of 31–32 mEq/kg. Thus, the CSF \( \text{HCO}_3^- \) concentration is normally about 7 mEq/kg lower than a passive relationship predicts. This is to say that there is a net electrochemical potential difference (\( \Delta \mu \)) for \( \text{H}^+ \) and \( \text{HCO}_3^- \) between CSF and blood that may be calculated from the equations

\[
\Delta \mu_{\text{H}^+} = 61.5 (\mu_{\text{H}^+} - \mu_{\text{H}^+_{\text{CSF}}}) + \Psi \quad (6)
\]

\[
\Delta \mu_{\text{HCO}_3^-} = 61.5 \log \frac{[\text{HCO}_3^-_{\text{CSF}}]}{[\text{HCO}_3^-_{\text{pl}}]} - \Psi \quad (7)
\]

where \( \Psi \) is the CSF/plasma potential. This \( \Delta \mu \) (for \( \text{H}^+ \)) represents a force that tends to drive \( \text{H}^+ \) from CSF to plasma, and the force will act so long as there is a net \( \Delta \mu \) remaining (i.e., until the CSF pH and \( \text{HCO}_3^- \) concentrations have reached the values required by a passive distribution). Since available evidence indicates that the blood–CSF barrier is at least slowly permeable to \( \text{H}^+ \) and \( \text{HCO}_3^- \), the \( \Delta \mu \) must lead to a continuous (passive) flow of \( \text{H}^+ \) from CSF to plasma. In order to maintain a steady state at a nonpassive distribution, another process must obviously create an opposite and equally large flow of \( \text{H}^+ \) into the CSF. In analogy with ion transport in other tissues, it has been assumed that this second process is an active secretion of \( \text{H}^+ \) from plasma to CSF.
which keeps pace with the passive movement of $H^+$ in the reverse direction. However, since the CSF faces not only the capillaries but also the cells of the tissue, the observed distribution of $H^+$ could also result if $H^+$ continuously leaks out from the cells, e.g., in the form of lactic acid. If this or a similar mechanism acidifies the CSF, active transport of $H^+$ (or $HCO_3^-$) need not necessarily be involved.

**Factors Influencing the CSF pH**

In order to discuss mechanisms that influence the pH of cerebral extracellular fluid we need to know not only the normal distribution of $H^+$ and $HCO_3^-$ between CSF and plasma but also the permeability of the CSF-plasma barriers to these ions, as well as to dissolved CO$_2$. The barriers are freely permeable to dissolved CO$_2$, a highly lipid-soluble molecule, but by most evidence appear to be sparingly permeable to hydrogen or bicarbonate ions. According to simple diffusion principles, therefore, as well as empirical findings, a change in plasma CO$_2$ tension is quickly transmitted to the CSF, while changes in plasma $HCO_3^-$ concentration are reflected in the CSF more slowly.

In seeming contradiction to the diffusion characteristics of the blood-CSF barrier, animal experiments demonstrate that acute hypercapnia is accompanied by a marked and fairly rapid accumulation of $HCO_3^-$ in the CSF. Thus, when rats are exposed to about 10 per cent CO$_2$, the CSF $HCO_3^-$ concentration increases by almost 10 mEq/l in 3 hours and by almost 20 mEq/l in 24 hours. If this extra $HCO_3^-$ emanates from plasma it would imply a fairly rapid bicarbonate flux between plasma and CSF. If, however, the source of the CSF $HCO_3^-$ is a carbonic anhydrase-dependent hydration of CO$_2$ in the choroid plexus (and glial) cells, as Maren's suggests, the findings do not necessarily indicate an ionic flux across the blood-CSF barrier. Thus, a final conclusion regarding $HCO_3^-$ exchanges between CSF and plasma must await rigorous testing of the hypothesis put forward by Maren.

If one holds in abeyance the improved concept of an active transport mechanism regulating the pH of CSF, three types of regulatory mechanisms remain. These include those associated with pH-dependent changes in pulmonary ventilation and in cerebral blood flow and that which manifests as a change in the CSF-to-plasma $HCO_3^-$ ratio.

Leusen reported almost 20 years ago that pulmonary ventilation increased when the cerebral ventricles were perfused with solutions high in P$_{CO_2}$ or low in [HCO$_3^-$]. These pioneering observations were soon confirmed and later results have suggested that there are chemoreceptor areas lying on the ventrolateral surface of the medulla that respond to changes in ECF pH. Subsequent studies by Pappenheimer and colleagues in unanesthetized goats and in man have beautifully demonstrated the exquisite sensitivity of a central chemoreceptor system to changes in CSF pH. In the goat, pulmonary ventilation increased from 5 to 45 l/min with a change in ECF pH of 0.15, and the entire range of ventilatory responses was obtained with a 0.2 pH change. The authors reported even greater sensitivity in man, in that a ventilatory increase from 3 to 30 l/min was elicited by an apparent change in CSF pH of only 0.05. Such ventilatory responses to change in CSF pH afford a powerful mechanism for the homeostatic regulation of CSF acid-base balance in any situation associated with nonrespiratory acidosis or alkalosis.

### Table 3. Acid–Base Values in Arterial, Venous, and Mean Capillary Plasma and Cisternal CSF

<table>
<thead>
<tr>
<th>Compartment</th>
<th>$P_{CO_2}$ (mm Hg)</th>
<th>$HCO_3^-$ (mEq/l)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial plasma</td>
<td>40.5</td>
<td>26.3</td>
<td>7.397</td>
</tr>
<tr>
<td>Venous plasma</td>
<td>50.5</td>
<td>28.4</td>
<td>7.337</td>
</tr>
<tr>
<td>Mean capillary plasma</td>
<td>45.5</td>
<td>27.4</td>
<td>7.367</td>
</tr>
<tr>
<td>Cisternal CSF</td>
<td>46.5</td>
<td>24.7</td>
<td>7.346</td>
</tr>
</tbody>
</table>

*The arterial plasma and CSF values were taken from v. Heijst et al., while the venous plasma and mean capillary plasma values were calculated as described in the text. The $HCO_3^-$ concentrations were expressed per kg of plasma water.*
Variations in cerebral blood flow in response to changes in CSF pH are quantitatively of less importance from a regulatory point of view, but cannot be entirely ignored. Experiments on animals and man demonstrate that CBF varies inversely with CSF pH. This relationship implies that hypercapnia is accompanied by a narrowed, and hypocapnia by a widened, difference in $P_{CO_2}$ between cerebral venous and arterial blood. In other words, the change in CBF attenuates the increase or decrease in $P_{CO_2}$ of the blood and, as a result, changes in CSF CO$_2$ tension (and pH) are proportionately less. The regulatory effect of such $P_{CO_2}$ changes will be moderate. In cerebral hypoxia, however, the CBF change is more important. In conditions causing cerebral hypoxia the anaerobic production of lactic acid by the brain tends to lower intracellular pH. As is discussed below, hyperventilation may efficiently limit the extent of such acidosis. Since lactic acid production is the result of cellular oxygen lack, however, the increase in CBF has the added benefit of enhancing the supply of oxygen to the tissue, thereby partially ameliorating the cause of the acidosis.

Changes in the HCO$_3^-$ ratio between CSF and plasma are known to occur primarily in nonrespiratory acid-base disorders and seem to represent a specific mechanism for the regulation of CSF pH. If CSF HCO$_3^-$ concentration always followed plasma [HCO$_3^-$] so that a CSF-to-plasma HCO$_3^-$ ratio of 0.90 were maintained, the regulation of CSF pH would be unspecific and dependent on the regulation of plasma pH. However, studies show that the ratio decreases in nonrespiratory alkalosis and increases in metabolic acidosis. In chronic conditions, the change in CSF HCO$_3^-$ concentration is only 30–40 per cent of the change in plasma [HCO$_3^-$], and the CSF-to-plasma HCO$_3^-$ ratio may therefore vary extensively.

It has been widely assumed that active transport of bicarbonate ion (or H$^+$) across the blood-CSF barrier is responsible for the "regulatory" change in the HCO$_3^-$ ratio during systemic acid-base changes. However, such conclusions have usually been drawn without due allowance for the change in the CSF–plasma d.c. potential difference. The d.c. potential varies inversely with the plasma pH, and the potential changes are upheld in chronic states. When the normal HCO$_3^-$ distribution between CSF and plasma is interpreted to show the presence of active transport of H$^+$ or HCO$_3^-$, the d.c. potential difference is taken into account. If we accept this argument we must also consider the influence of variations in d.c. potential in a changed acid-base state. We may then use equation 6 to calculate the expected CSF-to-plasma HCO$_3^-$ ratios at various plasma pH values, keeping $\Delta \mu$ constant. Such calculations show that variations of the CSF–plasma d.c. potential could explain most of the changes in the CSF-to-plasma HCO$_3^-$ ratio in respiratory acid-base changes. These HCO$_3^-$ changes would then be passive, in the sense that they depend on a d.c. potential change, and not on active transport of HCO$_3^-$ (or H$^+$).

**Respiratory Acid-Base Changes**

Figure 2, redrawn from reference 158, shows data for chronic respiratory acidosis and alkalosis in man, as reported from several sources. In drawing the figure the control values reported by the various authors were first corrected to a plasma pH of 7.40 and a CSF pH of 7.325, and the data thus give comparable figures for the deviations from normal in each set of values. The data for respiratory acidosis were obtained in patients with pulmonary insufficiency; those for respiratory alkalosis had various causes (hepatic disease, salicylism, pregnancy, arterial hypoxia due to pulmonary disease or high altitude). The results indicate that respiratory alkalosis is accompanied by fairly efficient regulation of CSF pH, while the regulation in respiratory acidosis is no better than the corresponding regulation of plasma pH. However, since the cases classified as such may not represent primary respiratory alkalosis, we treat arterial hypoxia and salicylism as special cases below.

Analysis of the data of figure 2 shows that respiratory acidosis in man is unaccompanied by any change in the HCO$_3^-$ ratio between CSF and plasma. Similar results have been
Fig. 2. Relation between pH of arterial blood and CSF p\(H\) in chronic respiratory acidosis and alkalosis. The symbols denote the mean values reported by the following authors: C Merwarth et al.,\textsuperscript{114} D Schwab,\textsuperscript{122} A Pauli et al.,\textsuperscript{134} \& Bühmann et al.,\textsuperscript{129} Mitchell et al.,\textsuperscript{122} X Posner et al.,\textsuperscript{141} C Huang and Lyons.\textsuperscript{17} Reproduced by permission from Kidney International.\textsuperscript{158}

Fig. 3. Relation between pH of arterial blood and CSF p\(H\) in chronic nonrespiratory acidosis and alkalosis. The symbols denote the mean values reported by the following authors: C Bradley and Semple,\textsuperscript{22} D Schwab,\textsuperscript{122} A Agrest et al.,\textsuperscript{1} A Pauli et al.,\textsuperscript{123} \& Bühmann et al.\textsuperscript{29} X Posner et al.,\textsuperscript{122} Mitchell et al.\textsuperscript{122} Reproduced by permission from Kidney International.\textsuperscript{158}

reported for chronic hypercapnia in experimental animals.\textsuperscript{3,10,147} As a result, the pH of CSF in chronic respiratory acidosis changes in proportion to plasma pH, and there seems to be no specific regulation of hydrogen ion concentration. This finding does not imply that the CSF HCO\(_3\)- concentration passively follows the plasma HCO\(_3\)- concentration, but rather that there are no mechanisms at hand capable of normalizing CSF pH. i.e., maintaining a higher HCO\(_3\)- concentration in CSF than in plasma in a steady state. Animal experiments demonstrate that CSF HCO\(_3\)- concentration in acute hypercapnia may increase more rapidly than plasma [HCO\(_3\)-]\textsuperscript{105-107} or even in the absence of a change in plasma [HCO\(_3\)-]\textsuperscript{113,135,162} In view of the fact that respiratory acidosis shifts the CSF/plasma d.c. potential towards a more positive value, it is tempting to ascribe this increase in CSF HCO\(_3\)- concentration to a passive equilibration along the electrochemical gradient. However, since a similar increase in the CSF-to-plasma HCO\(_3\)- ratio is observed in the cat, an animal that shows a negative shift in d.c. potential\textsuperscript{130} (unlike other mammals), other explanations must be sought. It is not necessary to invoke active transport of H\(^+\) or HCO\(_3\)-. As mentioned earlier, Maren\textsuperscript{168} considers the choroid plexus to secrete HCO\(_3\)- and suggests that the rate of secretion is proportional to the P\(_{CO}_2\). This interesting hypothesis would explain why CSF [HCO\(_3\)-] increases even when plasma [HCO\(_3\)-] remains constant. Unfortunately, it does not explain why chronic hypercapnia does not lead to an increased HCO\(_3\)- ratio between CSF and plasma unless it is assumed that the rate of HCO\(_3\)- secretion adapts in the chronic hypercapnic state.
NONRESPIRATORY ACID-BASE CHANGES

Most investigators agree that CSF pH shows a remarkable constancy in chronic systemic nonrespiratory acidosis and alkalosis (fig. 3). Acidosis is represented in figure 3 by renal insufficiency, and alkalosis by bicarbonate ingestion, aldosterone-secreting tumors, and hepatic disease. A similar constancy of CSF pH has been found in experimental animals rendered chemically acidic or alkalotic,\textsuperscript{33,38,141} as well as in man with other forms of metabolic acidosis, including most instances associated with diabetes or organic acid poisoning.\textsuperscript{10,99,142,144}

Opinions differ as to the sequence of events in nonrespiratory acidosis and alkalosis, and there is disagreement on mechanisms of regulation. To take metabolic acidosis as an example, Mitchell \textit{et al.}\textsuperscript{122} consider that the acidosis stimulates the peripheral chemoreceptors in the carotid and aortic bodies, and that the primary acid–base change in the CSF is a respiratory alkalosis. This alkalosis is then thought to be corrected by active transport of \( \text{HCO}_3^- \) from CSF to plasma. A different explanation has been proposed by Fencl \textit{et al.}\textsuperscript{58} Although a CSF alkalosis may apparently occur initially,\textsuperscript{31,44,105} Fencl \textit{et al.}\textsuperscript{58} maintain that it affects only large cavity fluid that exchanges \( \text{H}^+ \) and \( \text{HCO}_3^- \) slowly with plasma. The authors propose that the plasma acidosis is quickly transmitted to the narrow interstitial spaces around the respiratory neurons, and that the ventilatory increase is due to central acidosis. They conclude that the constancy of CSF pH is due both to the increased ventilation (and decrease in \( P_{\text{CO}_2} \)) and to active transport of \( \text{HCO}_3^- \) between plasma and CSF, the latter mechanism being responsible for the altered CSF-to-plasma \( \text{HCO}_3^- \) ratio.

Although definite proof is lacking, available data favor the view of Fencl \textit{et al.}\textsuperscript{58} Experiments on animals with metabolic acid–base changes studied in a steady state fail to show a CSF pH change opposite to that in plasma,\textsuperscript{33,38,141} making improbable any “paradoxical” acid–base change in the true ECF of brain. But the conclusion drawn by both groups of investigators of an active transport regulator of the \( \text{HCO}_3^- \) ratio has very little experimental support. If acidosis or alkalosis triggered a specific movement of \( \text{HCO}_3^- \) ions into or out of the CSF, respectively, the observed electrochemical potential difference should be grossly proportional to the rate of movement. In fact, calculations indicate that electrochemical potential differences for \( \text{H}^+ \) or \( \text{HCO}_3^- \) remain approximately constant in metabolic acidosis and alkalosis.\textsuperscript{121,158} As has been mentioned, however, changes in the CSF–plasma d.c. potential do occur in acidosis and alkalosis, and it remains a possibility that these changes may influence the altered \( \text{HCO}_3^- \) ratio.

METABOLIC ALKALOSIS

Mild metabolic alkalosis is, as a rule, accompanied by a relatively normal pH in the spinal fluid, along with evidence of some hypoventilation. However, severe metabolic alkalosis, such as occurs clinically with protracted vomiting or with the secretion or ingestion of corticosteroids, is accompanied by incomplete regulation of the pH of CSF, and the findings underscore the major role of respiratory compensation in CSF acid–base balance (table 4). With moderate systemic metabolic alkalosis, one sees in many patients a sequence in which the pH of CSF increases slightly and pulmonary ventilation declines. As a result, arterial oxygen tension decreases and \( \text{CO}_2 \) tension rises, minimizing the CSF pH change. This mechanism is self-limited because eventually the arterial oxygen tension decreases sufficiently to stimulate the peripheral respiratory chemoreceptors, precluding any further degree of hypoventilation with its alkalosis-compensating \( \text{CO}_2 \) retention. Under these circumstances, the bicarbonate concentration of CSF, although always lower than the plasma concentration, shows no tendency to fall independently of the plasma level, and the pH of CSF climbs considerably above its normal range, as indicated in table 4.\textsuperscript{102,137}

HYPOXIC HYPERVENTILATION

Since the peripheral chemoreceptors are very sensitive to arterial hypoxia, even moderate reductions in \( P_{\text{O}_2} \) induce an increase in ventilation and a consequent decrease in arterial \( \text{CO}_2 \) tension.\textsuperscript{29,32,54,107} Conversely, if the chemoreceptors are denervated, a de-
TABLE 4. Blood and CSF Acid–Base Values in Severe Metabolic Alkalosis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Arterial Blood</th>
<th>CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pH</td>
<td>P$_{co_2}$ (mm Hg)</td>
</tr>
<tr>
<td>Posner et al.</td>
<td>1</td>
<td>7.66</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>7.51</td>
</tr>
<tr>
<td>Lifschitz</td>
<td>3</td>
<td>7.59</td>
</tr>
</tbody>
</table>

crease in P$_{co_2}$ induces at least acutely a decrease in pulmonary ventilation, implying that hypoxia depresses central respiratory mechanisms. It has therefore seemed natural to regard hypoxic hyperventilation, whether caused by pulmonary disease or by residency at high altitudes, as being associated with a primary CSF alkalosis. Unfortunately, the available data on this important point are in conflict. One factor is that the ventilatory response to altitude reaches a maximum only after several weeks of exposure and differs between subjects native to sea level and high-altitude natives. Severinghaus and Carcelen found the CSF to be normal in sea-level natives kept chronically at high altitudes, and Blayo et al. reported the same thing. Dempsey and coworkers, however, recently reported that in both man and pony acclimatized to high altitudes the pH’s of CSF were 0.03–0.05 above sea-level values and, if anything, the degree of hyperventilation was in excess of that expected from hypoxic stimulation of the peripheral chemoreceptors alone. The discrepancy in findings illustrates the technical difficulties of such studies and emphasizes that physiologic conclusions about the results must remain tentative.

Several lines of evidence suggest that one of the stimuli for chronic hypoxic hyperventilation may arise directly from chemical changes occurring in brain itself. When goats are surgically deprived of their carotid chemoreceptors, they nevertheless hyperventilate when exposed chronically to hypoxia. Also, the CSF HCO$_3^-$ concentration in rabbits decreases during chronic hypoxia after total chemoreceptor denervation. These results indicate that neither the hyperventilation nor the decrease in CSF [HCO$_3^-$] depends entirely on the presence of a peripheral hypoxic chemoreceptor drive, and they leave central acidosis due to anaerobic production of lactic acid as an alternative explanation for at least part of the respiratory stimulation. In support of this, Sørensen and Milledge found that native high-altitude residents had a CSF pH that was more acid than normal, and it has been found that lactate accumulates in the CSF of animals when the P$_{co_2}$ is lowered below about 50 mm Hg.

**SALICYLATE INTOXICATION**

Salicylate intoxication is accompanied by hyperventilation and decreased arterial CO$_2$ tensions. Since neither section of the vagus nerves nor denervation of the carotid bodies halts the increase in ventilation, salicylates seem to exert their effects centrally. Experiments on goats have demonstrated that acute salicylate intoxication increases the CBF and cerebral metabolic rate of oxygen, both at normal and at decreased arterial CO$_2$ tensions, but the experiments failed to show a significant change in the pH of eisternal CSF. Measurements of CSF acid–base variables in patients with salicylate intoxication have shown that although a very few hypopneic patients have low pH values in the CSF, most show markedly increased pH values. This makes it difficult to conclude that cerebral extracellular acidosis is responsible for the hyperventilation. Several pieces of indirect or preliminary evidence, however, suggest that salicylism may produce an intracellular acidosis. In favor of this inference, adults with salicylism excrete a strongly acidic urine, and children with salicylate poisoning acutely develop systemic metabolic acidosis rather than respiratory alkalosis. Furthermore, recent (unpublished) results obtained in Siesjö’s laboratory demonstrate that acute salicylate intoxication in the rat is accompanied by
an intracellular acidosis in the brain. All these considerations suggest that the hyperventilation of salicylate intoxication may be stimulated by cerebral tissue acidosis, no matter what the pH of the bulk CSF fluid.

PASSIVE HYPERVENTILATION

As mentioned above, available data indicate that the regulation of CSF pH is mediated primarily via respiratory mechanisms and consequently is less efficient in respiratory acidosis than in nonrespiratory acidosis and alkalosis. These results suggest that a precise steady-state regulation of CSF pH can occur only in nonrespiratory acid–base disturbances, i.e., in conditions in which no limits are placed on naturally occurring respiratory regulation. Neither hypoxia nor salicylate intoxication unequivocally reflects CSF pH regulation in “pure” respiratory alkalosis, since both conditions may be associated with central acidosis; accordingly, it seems warranted to discuss experimental data on passive hyperventilation. Lensen, Posner and Plum, and Kazemi et al. hypoventilated dogs for periods as long as eight hours. Initially, the pH of CSF shifted substantially towards the alkaline side, then gradually returned towards more normal (but still elevated) values as a result of progressive lowering of CSF HCO₃⁻ concentration. In view of what has been discussed above, this lowering could have been due to 1) formation of lactic acid and titration of extracellular HCO₃⁻; 2) loss of HCO₃⁻ by means of diffusion to blood, and 3) reduced HCO₃⁻ secretion by plexus tissue and glial cells. Five to seven hours after the beginning of hyperventilation, however, the CSF pH at the cisterna magna was still significantly elevated in comparison with the normal values. Admittedly, these experiments do not represent chronic passive hyperventilation, and it cannot be excluded that further normalization would have occurred had the hyperventilation been prolonged. But the data are consistent with the hypothesis that full pH homeostasis of the cerebral extracellular fluids requires an uninhibited ventilatory response such as occurs in freely-breathing subjects with nonrespiratory acid–base abnormalities.

Concluding Remarks

There is now a wealth of information suggesting that the acid–base balance of cerebral extracellular fluids is regulated independently from that of blood, and that specific mechanisms may be involved. However, when one looks candidly at the available evidence, only the nonrespiratory acid–base disorders are characterized by CSF pH values close to normal. Thus, respiratory acidosis leads to shifts in the CSF pH that are as large as those in arterial blood, and two conditions that are usually classified as respiratory alkalosis (hypoxia and salicylate intoxication) may well represent cerebral acidosis of a nonrespiratory nature. This suggests that efficient pH regulation in the cerebral extracellular fluids occurs only in nonrespiratory acid–base disorders that allow full, physiologic, respiratory compensation. Since such acid–base disorders also lead to compensatory changes in the ratio between CSF and plasma HCO₃⁻, the ventilatory adjustments cannot entirely explain the constancy of CSF pH. It remains for future experiments to disclose the mechanisms behind the latter compensatory changes.

References

and composition of choroid plexus fluid. J Physiol (Lond) 181:516–524, 1965
23. Brightman MW: The intracerebral movement of proteins injected into blood and cerebro-
36. Cornese JJ Jr, Schmidt CF: The part played by reflexes from the carotid body in the chemical regulation of respiration in the dog. Am J Physiol 121:75–97, 1938


63. Flexner LB: Some problems of the origin, circulation and absorption of the cerebrospinal fluid. Q Rev Biol 8:397-422, 1933


71. Habert JC (editor): Cisternography and Hy-
drocephalus. Springfield, Ill., Charles C Thomas, 1972


120. Miner LC, Reed DJ: Composition of fluid obtained from choroid plexus tissue isolated in a chamber in situ. J Physiol 227:127–130, 1972


132. Pappenheimer JR, Heisey SR, Jordan EF, et


175. Watt JG, Dumske PR, Comroe JH Jr: Effects of inhalation of 100 per cent and 14 per cent oxygen upon respiration of unanesthetized dogs before and after chemoreceptor denervation. Am J Physiol 138:610–617, 1942–43


Fluids and Electrolytes

TOTAL AND EXCHANGEABLE BODY POTASSIUM Exchangeable body potassium measured by dilution techniques 24 hours after administration of 42K is commonly used to estimate total-body potassium. Evidence would suggest that equilibration of 42K is not complete until at least 40 hours after administration. A study was performed to compare total-body potassium measured by whole-body monitoring with that estimated by exchangeable potassium measured at 24 and 44 hours in a variety of patients. The authors also compared measured total-body potassium with that estimated from regression equations considering height, weight and age, or just height and age. They confirmed that equilibration was not complete at 24 hours, but when exchangeable potassium was expressed as either a percentage of total-body potassium or as mEq/kg, the mean values at 24 hours were not significantly different from those at 44 hours. In a hypokalemic patient, however, exchangeable potassium did not accurately reflect total-body potassium before treatment or when the patient was normokalemic. The authors conclude that: 1) an equilibration time of 24 hours is sufficient for practical purposes for measuring exchangeable potassium; 2) in patients with abnormal potassium metabolism, i.e., those most likely to be studied, equilibration may take longer and even then may not accurately reflect total-body potassium; 3) estimation of total-body potassium of obese patients is more accurate if weight is not involved in the regression equation. (Boddy, K., King, P. C., and Davies, D. L.: The Relationship Between Total Body Potassium and Exchangeable Body Potassium Measured at 24 Hours and 44 Hours after Administration of 42K. Eur J Clin Invest 3:188–192, 1973.)