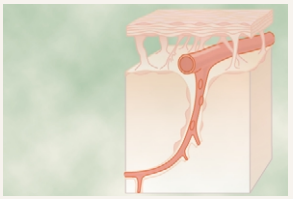
Cerebral Blood Flow, Cerebrospinal Fluid, and Brain Metabolism



Thus far, we have discussed the function of the brain as if it were independent of its blood flow, its metabolism, and its fluids. However, this is far from true because abnormalities of any of these can profoundly affect brain function. For instance, total cessation of blood flow to the brain causes unconsciousness within 5 to 10 seconds. This occurs because lack of oxygen delivery to the brain cells shuts down most metabolism in these cells. Also, on a longer time scale, abnormalities of the cerebrospinal fluid, either its composition or its fluid pressure, can have equally severe effects on brain function.

Cerebral Blood Flow

Normal Rate of Cerebral Blood Flow

Normal blood flow through the brain of the adult person averages 50 to 65 milliliters per 100 grams of brain tissue per minute. For the entire brain, this amounts to 750 to 900 ml/min, or 15 per cent of the resting cardiac output.

Regulation of Cerebral Blood Flow

As in most other vascular areas of the body, cerebral blood flow is highly related to metabolism of the tissue. At least three metabolic factors have potent effects in controlling cerebral blood flow: (1) carbon dioxide concentration, (2) hydrogen ion concentration, and (3) oxygen concentration.

Increase of Cerebral Blood Flow in Response to Excess Carbon Dioxide or Excess Hydrogen Ion Concentration. An increase in carbon dioxide concentration in the arterial blood perfusing the brain greatly increases cerebral blood flow. This is demonstrated in Figure 61–1, which shows that a 70 per cent increase in arterial P_{CO_2} approximately doubles cerebral blood flow.

Carbon dioxide is believed to increase cerebral blood flow by combining first with water in the body fluids to form carbonic acid, with subsequent dissociation of this acid to form hydrogen ions. The hydrogen ions then cause vasodilation of the cerebral vessels—the dilation being almost directly proportional to the increase in hydrogen ion concentration up to a blood flow limit of about twice normal.

Any other substance that increases the acidity of the brain tissue, and therefore increases hydrogen ion concentration, will likewise increase cerebral blood flow. Such substances include lactic acid, pyruvic acid, and any other acidic material formed during the course of tissue metabolism.

Importance of Cerebral Blood Flow Control by Carbon Dioxide and Hydrogen Ions. Increased hydrogen ion concentration greatly depresses neuronal activity. Therefore, it is fortunate that an increase in hydrogen ion concentration also causes an increase in blood flow, which in turn carries hydrogen ions, carbon dioxide, and other acid-forming substances away from the brain tissues. Loss of carbon dioxide removes carbonic acid from the tissues; this, along with removal of other acids, reduces the hydrogen ion concentration back toward normal. Thus, this mechanism helps maintain a constant hydrogen ion concentration in the cerebral fluids and thereby helps to maintain a normal, constant level of neuronal activity.

Oxygen Deficiency as a Regulator of Cerebral Blood Flow. Except during periods of intense brain activity, the rate of utilization of oxygen by the brain tissue remains within

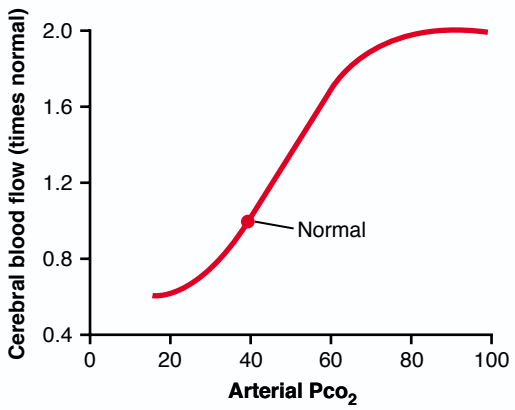


Figure 61–1

Relationship between arterial P_{CO_2} and cerebral blood flow.

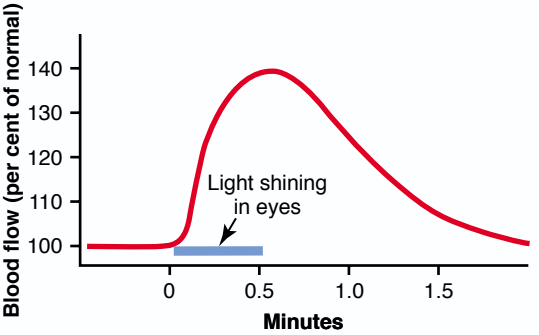


Figure 61–2

Increase in blood flow to the occipital regions of a cat's brain when light is shined into its eyes.

narrow limits—almost exactly 3.5 (± 0.2) milliliters of oxygen per 100 grams of brain tissue per minute. If blood flow to the brain ever becomes insufficient to supply this needed amount of oxygen, the oxygen deficiency mechanism for causing vasodilation immediately causes vasodilation, returning the brain blood flow and transport of oxygen to the cerebral tissues to near normal. Thus, this local blood flow regulatory mechanism is almost exactly the same in the brain as in coronary blood vessels, in skeletal muscle, and in most other circulatory areas of the body.

Experiments have shown that a decrease in cerebral *tissue* P_{O_2} below about 30 mm Hg (normal value is 35 to 40 mm Hg) immediately begins to increase cerebral blood flow. This is fortuitous because brain function becomes deranged at not much lower values of P_{O_2}, especially so at P_{O_2} levels below 20 mm Hg. Even coma can result at these low levels. Thus, the oxygen mechanism for local regulation of cerebral blood flow is a very important protective response against diminished cerebral neuronal activity and, therefore, against derangement of mental capability.

Measurement of Cerebral Blood Flow, and Effect of Brain Activity on the Flow. A method has been developed to record blood flow in as many as 256 isolated segments of the human cerebral cortex simultaneously. To do this, a radioactive substance, such as radioactive xenon, is injected into the carotid artery; then the radioactivity of each segment of the cortex is recorded as the radioactive substance passes through the brain tissue. For this purpose, 256 small radioactive scintillation detectors are pressed against the surface of the cortex. The rapidity of rise and decay of radioactivity in each tissue segment is a direct measure of the rate of blood flow through that segment.

Using this technique, it has become clear that blood flow in each individual segment of the brain changes as much as 100 to 150 per cent within seconds in response to changes in local neuronal activity. For instance, simply making a fist of the hand causes an immediate increase in blood flow in the motor cortex of the opposite side of the brain. Reading a book increases the blood flow, especially in the visual areas of the occipital cortex and in the language perception areas of the temporal cortex. This measuring procedure can also be used for localizing the origin of epileptic attacks because local brain blood flow increases acutely and markedly at the focal point of each attack.

Demonstrating the effect of local neuronal activity on cerebral blood flow, Figure 61–2 shows a typical increase in occipital blood flow recorded in a cat's brain when intense light is shined into its eyes for one-half minute.

Autoregulation of Cerebral Blood Flow When the Arterial Pressure Changes. Cerebral blood flow is "autoregulated" extremely well between arterial pressure limits of 60 and 140 mm Hg. That is, mean arterial pressure can be decreased acutely to as low as 60 mm Hg or increased to as high as 140 mm Hg without significant change in cerebral blood flow. And, in people who have hypertension, autoregulation of cerebral blood flow occurs even when the mean arterial pressure rises to as high as 160 to 180 mm Hg. This is demonstrated in Figure 61–3, which shows cerebral blood flow measured both in persons with normal blood pressure and in hypertensive and hypotensive patients. Note the extreme constancy of cerebral blood flow between the limits of 60 and 180 mm Hg mean arterial pressure. But, if the arterial pressure falls below 60 mm Hg, cerebral blood flow then does become severely decreased.

Role of the Sympathetic Nervous System in Controlling Cerebral Blood Flow. The cerebral circulatory system has strong sympathetic innervation that passes upward from the superior cervical sympathetic ganglia in the neck and then into the brain along with the cerebral arteries. This innervation supplies both the large brain arteries and the arteries that penetrate into the substance of the brain. However, transection of the sympathetic nerves or mild to moderate stimulation of them usually causes very little change in cerebral blood flow because the blood flow autoregulation mechanism can override the nervous effects.

When mean arterial pressure rises acutely to an exceptionally high level, such as during strenuous

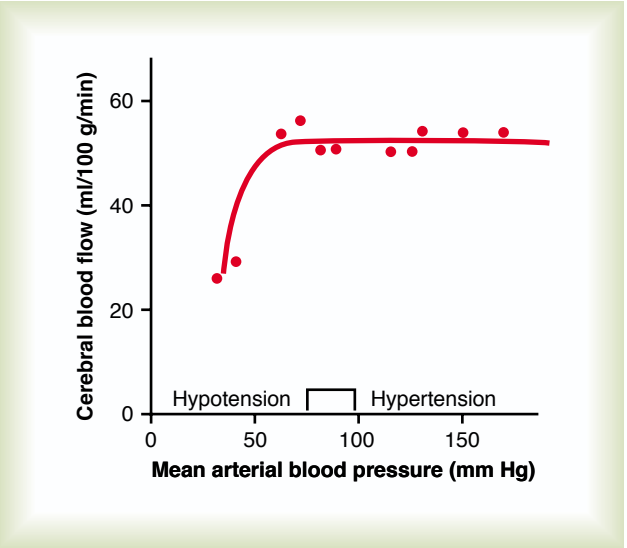


Figure 61–3

Effect of differences in mean arterial pressure, from hypotensive to hypertensive level, on cerebral blood flow in different human beings. (Modified from Lassen NA: Cerebral blood flow and oxygen consumption in man. Physiol Rev 39:183, 1959.)

exercise or during other states of excessive circulatory activity, the sympathetic nervous system normally constricts the large- and intermediate-sized brain arteries enough to prevent the high pressure from reaching the smaller brain blood vessels. This is important in preventing vascular hemorrhages into the brain—that is, for preventing the occurrence of "cerebral stroke."

Cerebral Microcirculation

As is true for almost all other tissues of the body, the number of blood capillaries in the brain is greatest where the metabolic needs are greatest. The overall metabolic rate of the brain gray matter where the neuronal cell bodies lie is about four times as great as that of white matter; correspondingly, the number of capillaries and rate of blood flow are also about four times as great in the gray matter.

An important structural characteristic of the brain capillaries is that they are much less "leaky" than the blood capillaries in almost any other tissue of the body. One reason for this is that the capillaries are supported on all sides by "glial feet," which are small projections from the surrounding glial cells that abut against all surfaces of the capillaries and provide physical support to prevent overstretching of the capillaries in case of high capillary blood pressure.

The walls of the small arterioles leading to the brain capillaries become greatly thickened in people who develop high blood pressure, and these arterioles remain significantly constricted all the time to prevent transmission of the high pressure to the capillaries. We shall see later in the chapter that whenever these systems for protecting against transudation of fluid into the brain break down, serious brain edema ensues, which can lead rapidly to coma and death.

Cerebral "Stroke" Occurs When Cerebral Blood Vessels Are Blocked

Almost all elderly people have blockage of some small arteries in the brain, and as many as 10 per cent eventually have enough blockage to cause serious disturbance of brain function, a condition called a "stroke."

Most strokes are caused by arteriosclerotic plaques that occur in one or more of the feeder arteries to the brain. The plaques can activate the clotting mechanism of the blood, causing a blood clot to occur and block blood flow in the artery, thereby leading to acute loss of brain function in a localized area.

In about one quarter of people who develop strokes, high blood pressure makes one of the blood vessels burst; hemorrhage then occurs, compressing the local brain tissue and further compromising its functions. The neurological effects of a stroke are determined by the brain area affected. One of the most common types of stroke is blockage of the *middle cerebral artery* that supplies the midportion of one brain hemisphere. For instance, if the middle cerebral artery is blocked on the left side of the brain, the person is likely to become almost totally demented because of lost function in Wernicke's speech comprehension area in the left cerebral hemisphere, and he or she also becomes unable to speak words because of loss of Broca's motor area for word formation. In addition, loss of function of neural motor control areas of the left hemisphere can create spastic paralysis of most muscles on the opposite side of the body.

In a similar manner, blockage of a *posterior cerebral artery* will cause infarction of the occipital pole of the hemisphere on the same side as the blockage, which causes loss of vision in both eyes in the half of the retina on the same side as the stroke lesion. Especially devastating are strokes that involve the blood supply to the midbrain because this can block nerve conduction in major pathways between the brain and spinal cord, causing *both sensory and motor abnormalities*.

Cerebrospinal Fluid System

The entire cerebral cavity enclosing the brain and spinal cord has a capacity of about 1600 to 1700 milliliters; about 150 milliliters of this capacity is occupied by *cerebrospinal fluid* and the remainder by the brain and cord. This fluid, as shown in Figure 61–4, is present in the *ventricles of the brain*, in the *cisterns around the outside of the brain*, and in the *subarachnoid space around both the brain and the spinal cord.* All these chambers are connected with one another, and the pressure of the fluid is maintained at a surprisingly constant level.

Cushioning Function of the Cerebrospinal Fluid

A major function of the cerebrospinal fluid is to cushion the brain within its solid vault. The brain and the cerebrospinal fluid have about the same specific gravity (only about 4 per cent different), so that the brain simply floats in the fluid. Therefore, a blow to the head, if it is not too intense, moves the entire brain simultaneously with the skull, causing no one portion of the brain to be momentarily contorted by the blow.

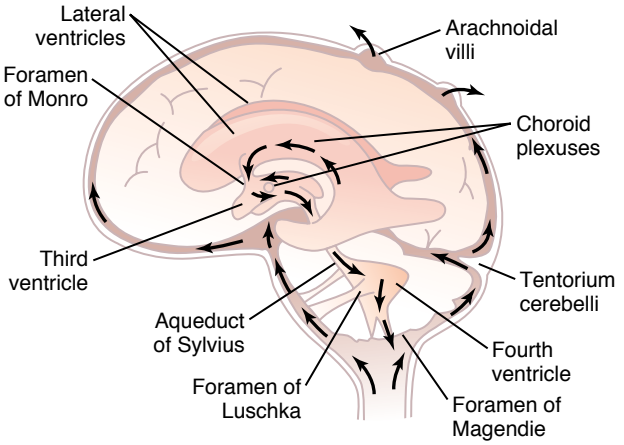


Figure 61–4

The arrows show the pathway of cerebrospinal fluid flow from the choroid plexuses in the lateral ventricles to the arachnoidal villi protruding into the dural sinuses.

Contrecoup. When a blow to the head is extremely severe, it may not damage the brain on the side of the head where the blow is struck but on the opposite side. This phenomenon is known as "contrecoup," and the reason for this effect is the following: When the blow is struck, the fluid on the struck side is so incompressible that as the skull moves, the fluid pushes the brain at the same time in unison with the skull. On the side opposite to the area that is struck, the sudden movement of the whole skull causes the skull to pull away from the brain momentarily because of the brain's inertia, creating for a split second a vacuum space in the cranial vault in the area opposite to the blow. Then, when the skull is no longer being accelerated by the blow, the vacuum suddenly collapses and the brain strikes the inner surface of the skull.

The poles and the inferior surfaces of the frontal and temporal lobes, where the brain comes into contact with bony protuberances in the base of the skull, are often the sites of injury and *contusions* (bruises) after a severe blow to the head, such as that experienced by a boxer. If the contusion occurs on the same side as the impact injury, it is a *coup injury*; if it occurs on the opposite side, the contusion is a *contrecoup injury*.

Formation, Flow, and Absorption of Cerebrospinal Fluid

Cerebrospinal fluid is formed at a rate of about 500 milliliters each day, which is three to four times as much as the total volume of fluid in the entire cerebrospinal fluid system. About two thirds or more of this fluid originates as *secretion from the choroid plexuses* in the four ventricles, *mainly in the two lateral ventricles*. Additional small amounts of fluid are secreted by the ependymal surfaces of all the ventricles and by the arachnoidal membranes; and a small amount comes from the brain itself through the perivascular spaces that surround the blood vessels passing through the brain.

The arrows in Figure 61–4 show that the main channels of fluid flow from the *choroid plexuses* and then through the cerebrospinal fluid system. The fluid secreted in the *lateral ventricles* passes first into the *third ventricle*; then, after addition of minute amounts of fluid

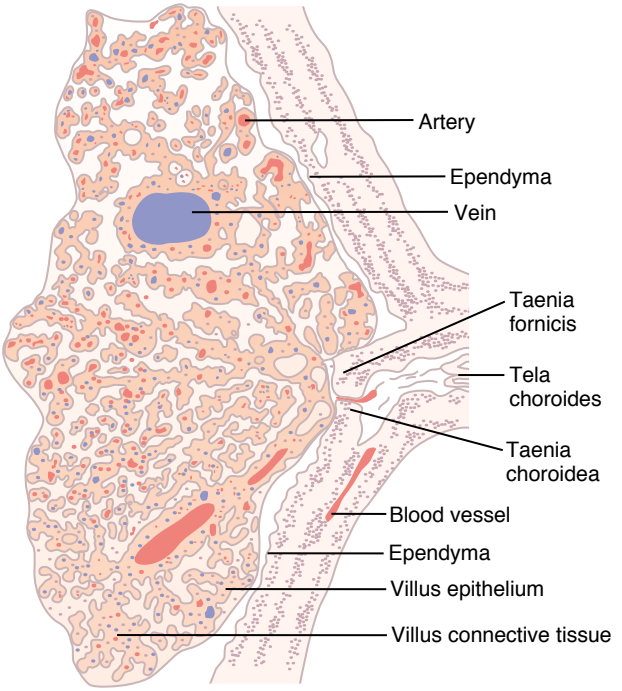


Figure 61–5

Choroid plexus in a lateral ventricle.

from the third ventricle, it flows downward along the *aqueduct of Sylvius* into the *fourth ventricle*, where still another minute amount of fluid is added. Finally, the fluid passes out of the fourth ventricle through three small openings, *two lateral foramina of Luschka* and a *midline foramen of Magendie*, entering the *cisterna magna*, a fluid space that lies behind the medulla and beneath the cerebellum.

The cisterna magna is continuous with the *subarachnoid space* that surrounds the entire brain and spinal cord. Almost all the cerebrospinal fluid then flows upward from the cisterna magna through the subarachnoid spaces surrounding the cerebrum. From here, the fluid flows into and through multiple *arachnoidal villi* that project into the large sagittal venous sinus and other venous sinuses of the cerebrum. Thus, any extra fluid empties into the venous blood through pores of these villi.

Secretion by the Choroid Plexus. The *choroid plexus*, a section of which is shown in Figure 61–5, is a cauliflower-like growth of blood vessels covered by a thin layer of epithelial cells. This plexus projects into (1 and 2) the temporal horn of each lateral ventricle, (3) the posterior portion of the third ventricle, and (4) the roof of the fourth ventricle.

Secretion of fluid into the ventricles by the choroid plexus depends mainly on active transport of sodium ions through the epithelial cells lining the outside of the plexus. The sodium ions in turn pull along large amounts of chloride ions as well because the positive charge of the sodium ion attracts the chloride ion's negative charge. The two of these together increase the quantity of osmotically active sodium chloride in the cerebrospinal fluid, which then causes almost immediate osmosis of water through the membrane, thus providing the fluid of the secretion.

Less important transport processes move small amounts of glucose into the cerebrospinal fluid and both potassium and bicarbonate ions out of the cerebrospinal fluid into the capillaries. Therefore, the resulting characteristics of the cerebrospinal fluid become the following: osmotic pressure, approximately equal to that of plasma; sodium ion concentration, also approximately equal to that of plasma; chloride ion, about 15 per cent greater than in plasma; potassium ion, approximately 40 per cent less; and glucose, about 30 per cent less.

Absorption of Cerebrospinal Fluid Through the Arachnoidal Villi. The *arachnoidal villi* are microscopic fingerlike inward projections of the arachnoidal membrane through the walls and into the venous sinuses. Conglomerates of these villi form macroscopic structures called *arachnoidal granulations* that can be seen protruding into the sinuses. The endothelial cells covering the villi have been shown by electron microscopy to have vesicular passages directly through the bodies of the cells large enough to allow relatively free flow of (1) cerebrospinal fluid, (2) dissolved protein molecules, and (3) even particles as large as red and white blood cells into the venous blood.

Perivascular Spaces and Cerebrospinal Fluid. The large arteries and veins of the brain lie on the surface of the brain but their ends penetrate inward, carrying with them a layer of *pia mater,* the membrane that covers the brain, as shown in Figure 61–6. The pia is only loosely adherent to the vessels, so that a space, the *perivascular space,* exists between it and each vessel. Therefore, perivascular spaces follow both the arteries and the veins into the brain as far as the arterioles and venules go.

Lymphatic Function of the Perivascular Spaces. As is true elsewhere in the body, a small amount of protein leaks out of the brain capillaries into the interstitial spaces of the brain. Because no true lymphatics are present in brain tissue, excess protein in the brain tissue leaves the tissue flowing with fluid through the perivascular spaces into the subarachnoid spaces. On reaching the subarachnoid spaces, the protein then flows with the cerebrospinal fluid, to be absorbed through the *arachnoidal villi* into the large cerebral veins. Therefore, perivascular spaces, in effect, are a specialized lymphatic system for the brain.

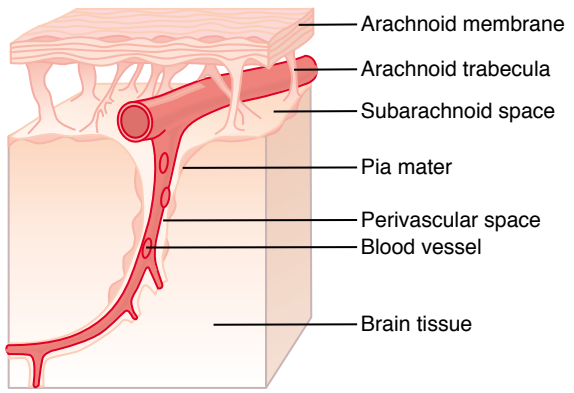


Figure 61–6

Drainage of a perivascular space into the subarachnoid space. (Redrawn from Ranson SW, Clark SL: Anatomy of the Nervous System. Philadelphia: WB Saunders Co, 1959.)

In addition to transporting fluid and proteins, the perivascular spaces transport extraneous particulate matter out of the brain. For instance, whenever infection occurs in the brain, dead white blood cells and other infectious debris are carried away through the perivascular spaces.

Cerebrospinal Fluid Pressure

The normal pressure in the cerebrospinal fluid system *when one is lying in a horizontal position* averages 130 millimeters of water (10 mm Hg), although this may be as low as 65 millimeters of water or as high as 195 millimeters of water even in the normal healthy person.

Regulation of Cerebrospinal Fluid Pressure by the Arachnoidal Villi. The normal rate of cerebrospinal fluid formation remains very nearly constant, so that changes in fluid formation are seldom a factor in pressure control. Conversely, the arachnoidal villi function like "valves" that allow cerebrospinal fluid and its contents to flow readily into the blood of the venous sinuses while not allowing blood to flow backward in the opposite direction. Normally, this valve action of the villi allows cerebrospinal fluid to begin to flow into the blood when cerebrospinal fluid pressure is about 1.5 mm Hg greater than the pressure of the blood in the venous sinuses. Then, if the cerebrospinal fluid pressure rises still higher, the valves open more widely, so that under normal conditions, the cerebrospinal fluid pressure almost never rises more than a few millimeters of mercury higher than the pressure in the cerebral venous sinuses.

Conversely, in disease states, the villi sometimes become blocked by large particulate matter, by fibrosis, or by excesses of blood cells that have leaked into the cerebrospinal fluid in brain diseases. Such blockage can cause high cerebrospinal fluid pressure, as follows.

High Cerebrospinal Fluid Pressure in Pathological Conditions of the Brain. Often a large *brain tumor* elevates the cerebrospinal fluid pressure by decreasing reabsorption of the cerebrospinal fluid back into the blood. As a result, the cerebrospinal fluid pressure can rise to as much as 500 millimeters of water (37 mm Hg) or about four times normal.

The cerebrospinal fluid pressure also rises considerably when *hemorrhage* or *infection* occurs in the cranial vault. In both these conditions, large numbers of red and/or white blood cells suddenly appear in the cerebrospinal fluid, and they can cause serious blockage of the small absorption channels through the arachnoidal villi. This also sometimes elevates the cerebrospinal fluid pressure to 400 to 600 millimeters of water (about four times normal).

Some babies are born with high cerebrospinal fluid pressure. This is often caused by abnormally high resistance to fluid reabsorption through the arachnoidal villi, resulting either from too few arachnoidal villi or from villi with abnormal absorptive properties. This is discussed later in connection with *hydrocephalus.*

Measurement of Cerebrospinal Fluid Pressure. The usual procedure for measuring cerebrospinal fluid pressure is very simple and is the following: First, the person lies exactly horizontally on his or her side so that the fluid

pressure in the spinal canal is equal to the pressure in the cranial vault. A spinal needle is then inserted into the lumbar spinal canal below the lower end of the cord, and the needle is connected to a vertical glass tube that is open to the air at its top. The spinal fluid is allowed to rise in the tube as high as it will. If it rises to a level 136 millimeters above the level of the needle, the pressure is said to be 136 millimeters of water pressure or, dividing this by 13.6, which is the specific gravity of mercury, about 10 mm Hg pressure.

High Cerebrospinal Fluid Pressure Causes Edema of the Optic Disc—Papilledema. Anatomically, the dura of the brain extends as a sheath around the optic nerve and then connects with the sclera of the eye. When the pressure rises in the cerebrospinal fluid system, it also rises inside the optic nerve sheath. The retinal artery and vein pierce this sheath a few millimeters behind the eye and then pass along with the optic nerve fibers into the eye itself. Therefore, (1) high cerebrospinal fluid pressure pushes fluid first into the optic nerve sheath and then along the spaces between the optic nerve fibers to the interior of the eyeball; (2) the high pressure decreases outward fluid flow in the optic nerves, causing accumulation of excess fluid in the optic disc at the center of the retina; and (3) the pressure in the sheath also impedes flow of blood in the retinal vein, thereby increasing the retinal capillary pressure throughout the eye, which results in still more retinal edema.

The tissues of the optic disc are much more distensible than those of the remainder of the retina, so that the disc becomes far more edematous than the remainder of the retina and swells into the cavity of the eye. The swelling of the disc can be observed with an ophthalmoscope and is called *papilledema.* Neurologists can estimate the cerebrospinal fluid pressure by assessing the extent to which the edematous optic disc protrudes into the eyeball.

Obstruction to Flow of Cerebrospinal Fluid Can Cause Hydrocephalus

"Hydrocephalus" means excess water in the cranial vault. This condition is frequently divided into *communicating hydrocephalus* and *noncommunicating hydrocephalus.* In communicating hydrocephalus fluid flows readily from the ventricular system into the subarachnoid space, whereas in noncommunicating hydrocephalus fluid flow out of one or more of the ventricles is blocked.

Usually the *noncommunicating* type of hydrocephalus is caused by a *block in the aqueduct of Sylvius*, resulting from *atresia* (closure) before birth in many babies or from blockage by a brain tumor at any age. As fluid is formed by the choroid plexuses in the two lateral and the third ventricles, the volumes of these three ventricles increase greatly. This flattens the brain into a thin shell against the skull. In neonates, the increased pressure also causes the whole head to swell because the skull bones have not yet fused.

The *communicating* type of hydrocephalus is usually caused by blockage of fluid flow in the subarachnoid spaces around the basal regions of the brain or by blockage of the arachnoidal villi where the fluid is normally absorbed into the venous sinuses. Fluid therefore collects both on the outside of the brain and to a lesser extent inside the ventricles. This will also cause the head to swell tremendously if it occurs in infancy when the skull is still pliable and can be stretched, and it can damage the brain at any age. A therapy for many types of hydrocephalus is surgical placement of a silicone tube shunt all the way from one of the brain ventricles to the peritoneal cavity where the excess fluid can be absorbed into the blood.

Blood–Cerebrospinal Fluid and Blood-Brain Barriers

It has already been pointed out that the concentrations of several important constituents of cerebrospinal fluid are not the same as in extracellular fluid elsewhere in the body. Furthermore, many large molecular substances hardly pass at all from the blood into the cerebrospinal fluid or into the interstitial fluids of the brain, even though these same substances pass readily into the usual interstitial fluids of the body. Therefore, it is said that barriers, called the *blood–cerebrospinal fluid barrier* and the *blood-brain barrier*, exist between the blood and the cerebrospinal fluid and brain fluid, respectively.

Barriers exist both at the choroid plexus and at the tissue capillary membranes in essentially all areas of the brain parenchyma *except in some areas of the hypothalamus*, *pineal gland*, and *area postrema*, where substances diffuse with greater ease into the tissue spaces. The ease of diffusion in these areas is important because they have sensory receptors that respond to specific changes in the body fluids, such as changes in osmolality and in glucose concentration, as well as receptors for peptide hormones that regulate thirst, such as angiotensin II. The blood-brain barrier also has specific carrier molecules that facilitate transport of hormones, such as leptin, from the blood into the hypothalamus where they bind to specific receptors that control other functions such as appetite and sympathetic nervous system activity.

In general, the blood–cerebrospinal fluid and blood-brain barriers are highly permeable to water, carbon dioxide, oxygen, and most lipid-soluble substances such as alcohol and anesthetics; slightly permeable to electrolytes such as sodium, chloride, and potassium; and almost totally impermeable to plasma proteins and most non–lipid-soluble large organic molecules. Therefore, the blood–cerebrospinal fluid and blood-brain barriers often make it impossible to achieve effective concentrations of therapeutic drugs, such as protein antibodies and non–lipid-soluble drugs, in the cerebrospinal fluid or parenchyma of the brain.

The cause of the low permeability of the blood–cerebrospinal fluid and blood-brain barriers is the manner in which the endothelial cells of the brain tissue capillaries are joined to one another. They are joined by so-called *tight junctions.* That is, the membranes of the adjacent endothelial cells are tightly fused rather than having large slit-pores between them, as is the case for most other capillaries of the body.

Brain Edema

One of the most serious complications of abnormal cerebral fluid dynamics is the development of *brain edema.* Because the brain is encased in a solid cranial vault, accumulation of extra edema fluid compresses the

blood vessels, often causing seriously decreased blood flow and destruction of brain tissue.

The usual cause of brain edema is either greatly increased capillary pressure or damage to the capillary wall that makes the wall leaky to fluid. A very common cause is a serious blow to the head, leading to *brain concussion*, in which the brain tissues and capillaries are traumatized so that capillary fluid leaks into the traumatized tissues.

Once brain edema begins, it often initiates two vicious circles because of the following positive feedbacks: (1) Edema compresses the vasculature. This in turn decreases blood flow and causes brain ischemia. The ischemia in turn causes arteriolar dilation with still further increase in capillary pressure. The increased capillary pressure then causes more edema fluid, so that the edema becomes progressively worse. (2) The decreased cerebral blood flow also decreases oxygen delivery. This increases the permeability of the capillaries, allowing still more fluid leakage. It also turns off the sodium pumps of the neuronal tissue cells, thus allowing these cells to swell in addition.

Once these two vicious circles have begun, heroic measures must be used to prevent total destruction of the brain. One such measure is to infuse intravenously a concentrated osmotic substance, such as a very concentrated mannitol solution. This pulls fluid by osmosis from the brain tissue and breaks up the vicious circles. Another procedure is to remove fluid quickly from the lateral ventricles of the brain by means of ventricular needle puncture, thereby relieving the intracerebral pressure.

Brain Metabolism

Like other tissues, the brain requires oxygen and food nutrients to supply its metabolic needs. However, there are special peculiarities of brain metabolism that require mention.

Total Brain Metabolic Rate and Metabolic Rate of Neurons. Under resting but awake conditions, the metabolism of the brain accounts for about 15 per cent of the total metabolism in the body, even though the mass of the brain is only 2 per cent of the total body mass. Therefore, under resting conditions, brain metabolism per unit mass of tissue is about 7.5 times the average metabolism in non–nervous system tissues.

Most of this excess metabolism of the brain occurs in the neurons, not in the glial supportive tissues. The major need for metabolism in the neurons is to pump ions through their membranes, mainly to transport sodium and calcium ions to the outside of the neuronal membrane and potassium ions to the interior. Each time a neuron conducts an action potential, these ions move through the membranes, increasing the need for additional membrane transport to restore proper ionic concentration differences across the neuron membranes. Therefore, during excessive brain activity, neuronal metabolism can increase as much as 100 to 150 per cent.

Special Requirement of the Brain for Oxygen—Lack of Significant Anaerobic Metabolism. Most tissues of the body can live without oxygen for several minutes and some for as long as 30 minutes. During this time, the tissue cells obtain their energy through processes of anaerobic metabolism, which means release of energy by partially breaking down glucose and glycogen but without combining these with oxygen. This delivers energy only at the expense of consuming tremendous amounts of glucose and glycogen. However, it does keep the tissues alive.

The brain is not capable of much anaerobic metabolism. One of the reasons for this is the high metabolic rate of the neurons, so that most neuronal activity depends on second-by-second delivery of oxygen from the blood. Putting these factors together, one can understand why sudden cessation of blood flow to the brain or sudden total lack of oxygen in the blood can cause unconsciousness within 5 to 10 seconds.

Under Normal Conditions Most Brain Energy Is Supplied by Glucose. Under normal conditions, almost all the energy used by the brain cells is supplied by glucose derived from the blood. As is true for oxygen, most of this is derived minute by minute and second by second from the capillary blood, with a total of only about a 2-minute supply of glucose normally stored as glycogen in the neurons at any given time.

A special feature of glucose delivery to the neurons is that its transport into the neurons through the cell membrane is not dependent on insulin, even though insulin is required for glucose transport into most other body cells. Therefore, in patients who have serious diabetes with essentially zero secretion of insulin, glucose still diffuses readily into the neurons—which is most fortunate in preventing loss of mental function in diabetic patients. Yet, when a diabetic patient is overtreated with insulin, the blood glucose concentration can fall extremely low because the excess insulin causes almost all the glucose in the blood to be transported rapidly into the vast numbers of insulin-sensitive non-neural cells throughout the body, especially into muscle and liver cells. When this happens, not enough glucose is left in the blood to supply the neurons properly, and mental function does then become seriously deranged, leading sometimes to coma and even more often to mental imbalances and psychotic disturbances—all caused by overtreatment with insulin.

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