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Causes of Neurogenic Shock. Some neurogenic factors that can cause loss of vasomotor tone include the following:

1. *Deep general anesthesia* often depresses the vasomotor center enough to cause vasomotor paralysis, with resulting neurogenic shock.
2. *Spinal anesthesia*, especially when this extends all the way up the spinal cord, blocks the sympathetic nervous outflow from the nervous system and can be a potent cause of neurogenic shock.
3. *Brain damage* is often a cause of vasomotor paralysis. Many patients who have had a brain concussion or contusion of the basal regions of the brain experience profound neurogenic shock. Also, even though brain ischemia for a few minutes almost always causes extreme vasomotor stimulation and increased blood pressure, prolonged ischemia (lasting >5–10 minutes) can cause the opposite effect—total inactivation of the vasomotor neurons in the brain stem, with a consequent decrease in arterial pressure and development of severe neurogenic shock.

ANAPHYLACTIC SHOCK AND HISTAMINE SHOCK

Anaphylaxis is an allergic condition in which cardiac output and arterial pressure often decrease drastically. This condition is discussed in Chapter 35. It results primarily from an antigen-antibody reaction that rapidly occurs after an antigen to which the person is sensitive enters the circulation. One of the principal effects is to cause the *basophils* in the blood and *mast* cells in the pericapillary tissues to release *histamine* or a *histamine-like substance*. The histamine causes the following: (1) an increase in vascular capacity because of venous dilation, thus causing a marked decrease in venous return; (2) dilation of the arterioles, resulting in greatly reduced arterial pressure; and (3) greatly increased capillary permeability, with rapid loss of fluid and protein into the tissue spaces. The net effect is a great reduction in venous return and, sometimes, such serious shock that the person may die within minutes.

Intravenous injection of large amounts of histamine causes histamine shock, which has characteristics almost identical to those of anaphylactic shock.

SEPTIC SHOCK

Septic shock refers to a bacterial infection widely disseminated to many areas of the body, with the infection being carried through the blood from one tissue to another and causing extensive damage. There are many varieties of septic shock because of the many types of bacterial infections that can cause it, and because infection in different parts of the body produces different effects. Most cases of septic shock, however, are caused by Gram-positive bacteria, followed by endotoxin-producing Gram-negative bacteria.

Septic shock is extremely important to the clinician because, other than cardiogenic shock, septic shock is currently the most frequent cause of shock-related death in the hospital.

Some of the typical causes of septic shock include the following:

1. Peritonitis caused by spread of infection from the uterus and fallopian tubes, sometimes resulting from an instrumental abortion performed under unsterile conditions
2. Peritonitis resulting from rupture of the gastrointestinal system, sometimes caused by intestinal disease or by wounds
3. Generalized bodily infection resulting from spread of a skin infection such as streptococcal or staphylococcal infection
4. Generalized gangrenous infection resulting specifically from gas gangrene bacilli, spreading first through peripheral tissues and finally via the blood to the internal organs, especially the liver
5. Infection spreading into the blood from the kidney or urinary tract, often caused by colon bacilli.

Special Features of Septic Shock. Because of the multiple types of septic shock, it is difficult to categorize this condition. The following features are often observed:

1. High fever
2. Often marked vasodilation throughout the body, especially in the infected tissues
3. High cardiac output in perhaps half of patients, caused by arteriolar dilation in the infected tissues and by high metabolic rate and vasodilation elsewhere in the body, resulting from bacterial toxin stimulation of cellular metabolism and from a high body temperature
4. Sludging of the blood, caused by red cell agglutination in response to degenerating tissues
5. Development of micro–blood clots in widespread areas of the body, a condition called *disseminated intravascular coagulation*; also, this causes the blood clotting factors to be used up, so hemorrhaging occurs in many tissues, especially in the gut wall of the intestinal tract

In early stages of septic shock, the patient usually does not have signs of circulatory collapse but only signs of the bacterial infection. As the infection becomes more severe, the circulatory system usually becomes involved because of direct extension of the infection or secondarily as a result of toxins from the bacteria, with resultant loss of plasma into the infected tissues through deteriorating blood capillary walls. There finally comes a point at which deterioration of the circulation becomes progressive in the same way that progression occurs in all other types of shock. The end stages of septic shock are not greatly different from the end stages of hemorrhagic shock, even though the initiating factors are markedly different in the two conditions.

PHYSIOLOGY OF TREATMENT IN SHOCK

REPLACEMENT THERAPY

Blood and Plasma Transfusion. If a person is in shock caused by hemorrhage, the best possible therapy is usually transfusion of whole blood. If the shock is caused by plasma loss, the best therapy is administration of plasma. When dehydration is the cause, administration of an appropriate electrolyte solution can correct the shock.

Whole blood is not always available, such as under battlefield conditions. Plasma can usually substitute adequately for whole blood because it increases the blood volume and restores normal hemodynamics. Plasma cannot restore a normal hematocrit, but the body can usually stand a decrease in hematocrit to about half of normal before serious consequences result if cardiac output is adequate. Therefore, in emergency conditions, it is reasonable to use plasma in place of whole blood for treatment of hemorrhagic or most other types of hypovolemic shock.

Sometimes, plasma is unavailable. In these cases, various *plasma substitutes* have been developed that perform almost exactly the same hemodynamic functions as plasma. One of these substitutes is dextran solution.

Dextran Solution as a Plasma Substitute. The principal requirement of a truly effective plasma substitute is that it remain in the circulatory system—that is, it does not filter through the capillary pores into the tissue spaces. In addition, the solution must be nontoxic and must contain appropriate electrolytes to prevent derangement of the body's extracellular fluid electrolytes on administration.

To remain in the circulation, the plasma substitute must contain some substance that has a large enough molecular size to exert colloid osmotic pressure. One substance developed for this purpose is *dextran,* a large polysaccharide polymer of glucose. Dextrans of appropriate molecular size do not pass through the capillary pores and, therefore, can replace plasma proteins as colloid osmotic agents.

Few toxic reactions have been observed when using purified dextran to provide colloid osmotic pressure; therefore, solutions containing this substance have been used as a substitute for plasma in fluid replacement therapy.

TREATMENT OF NEUROGENIC AND ANAPHYLACTIC SHOCK WITH SYMPATHOMIMETIC DRUGS

A *sympathomimetic drug* is a drug that mimics sympathetic stimulation. These drugs include *norepinephrine, epinephrine,* and a large number of long-acting drugs that have the same basic effects as epinephrine and norepinephrine.

In two types of shock, sympathomimetic drugs have proven to be especially beneficial. The first of these is *neurogenic shock,* in which the sympathetic nervous system is severely depressed. Administering a sympathomimetic drug takes the place of the diminished sympathetic actions and can often restore full circulatory function.

The second type of shock in which sympathomimetic drugs are valuable is *anaphylactic shock,* in which excess histamine plays a prominent role. The sympathomimetic drugs have a vasoconstrictor effect that opposes the vasodilating effect of histamine. Therefore, epinephrine, norepinephrine, or other sympathomimetic drugs are often lifesaving.

Sympathomimetic drugs have not proved to be very valuable in hemorrhagic shock. The reason is that in this type of shock, the sympathetic nervous system is almost always maximally activated by the circulatory reflexes; so much norepinephrine and epinephrine are already circulating in the blood that sympathomimetic drugs have essentially no additional beneficial effect.

OTHER THERAPY

Treatment by the Head-Down Position. When the pressure falls too low in most types of shock, especially in hemorrhagic and neurogenic shock, placing the patient with the head at least 12 inches lower than the feet helps in promoting venous return, thereby also increasing cardiac output. This head-down position is the first essential step in the treatment of many types of shock.

Oxygen Therapy. Because a major deleterious effect of most types of shock is too little delivery of oxygen to the tissues, giving the patient oxygen to breathe can be of benefit in some cases. However, this intervention frequently is far less beneficial than one might expect because the problem in most types of shock is not inadequate oxygenation of the blood by the lungs but inadequate transport of the blood after it is oxygenated.

Treatment With Glucocorticoids. Glucocorticoids—adrenal cortex hormones that control glucose metabolism—are frequently given to patients in severe shock for several reasons: (1) experiments have shown empirically that glucocorticoids frequently increase the strength of the heart in the late stages of shock; (2) glucocorticoids stabilize lysosomes in tissue cells and thereby prevent the release of lysosomal enzymes into the cytoplasm of the cells, thus preventing deterioration from this source; and (3) glucocorticoids might aid in the metabolism of glucose by the severely damaged cells.

CIRCULATORY ARREST

A condition closely allied to circulatory shock is circulatory arrest, in which all blood flow stops. This condition can occur, for example, as a result of *cardiac arrest* or *ventricular fibrillation.*

Ventricular fibrillation can usually be stopped by strong electroshock of the heart, the basic principles of which are described in Chapter 13.

In the case of complete cardiac arrest, a normal cardiac rhythm can sometimes be restored by immediately applying cardiopulmonary resuscitation procedures while at the same time supplying the patient's lungs with adequate quantities of ventilatory oxygen.

Effect of Circulatory Arrest on the Brain

A special challenge in circulatory arrest is to prevent detrimental effects of the arrest on the brain. In general, more than 5 to 8 minutes of total circulatory arrest can cause at least some degree of permanent brain damage in more than half of patients. Circulatory arrest for as long as 10 to 15 minutes almost always permanently destroys significant amounts of mental capacity.

For many years, it was thought that this detrimental effect on the brain was caused by the acute cerebral hypoxia that occurs during circulatory arrest. However, experiments have shown that if blood clots are prevented from occurring in the blood vessels of the brain, this will also prevent much of the early deterioration of the brain during circulatory arrest. For example, in animal experiments, all the blood was removed from the animal's blood vessels at the beginning of circulatory arrest and then replaced at the end of circulatory arrest so that no intravascular blood clotting could occur. In this experiment, the brain was usually able to withstand up to 30 minutes of circulatory arrest without permanent brain damage. Also, administration of heparin or streptokinase (to prevent blood coagulation) before cardiac arrest was shown to increase the survivability of the brain up to two to four times longer than usual.

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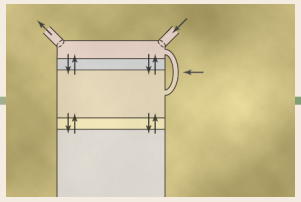

CHAPTER 25

UNIT V

Regulation of Body Fluid Compartments: Extracellular and Intracellular Fluids; Edema

The maintenance of a relatively constant volume and stable composition of the body fluids is essential for homeostasis. Some of the most common and important problems in clinical medicine arise because of abnormalities in the control systems that maintain this relative constancy of the body fluids. In this chapter and in the following chapters on the kidneys, we discuss overall regulation of body fluid volume, constituents of the extracellular fluid, acid–base balance, and control of fluid exchange between extracellular and intracellular compartments.

FLUID INTAKE AND OUTPUT ARE BALANCED DURING STEADY-STATE CONDITIONS

The relative constancy of the body fluids is remarkable, because there is continuous exchange of fluid and solutes with the external environment, as well as within the different body compartments. For example, fluid added to the body is highly variable and must be carefully matched by an equal output of water from the body to prevent body fluid volumes from increasing or decreasing.

DAILY INTAKE OF WATER

Water is added to the body by two major sources: (1) it is ingested in the form of liquids or water in food, which together normally add about 2100 ml/day to the body fluids; and (2) it is synthesized in the body by oxidation of carbohydrates, adding about 200 ml/day. These mechanisms provide a total water intake of about 2300 ml/day (**Table 25-1**). However, intake of water is highly variable among different people and even within the same person on different days, depending on climate, habits, and level of physical activity.

DAILY LOSS OF BODY WATER

Insensible Water Loss. Some water losses cannot be precisely regulated. For example, humans experience continuous water loss by evaporation from the respiratory tract and diffusion through the skin, which together account for about 700 ml/day of water loss under normal conditions. This loss is termed *insensible water loss* because we are not consciously aware of it, even though it occurs continually in all living people.

Insensible water loss through the skin occurs independently of sweating and is present even in people who are born without sweat glands; the average water loss by diffusion through the skin is about 300 to 400 ml/day. This loss is minimized by the cholesterol-filled, cornified layer of the skin, which provides a barrier against excessive loss by diffusion. When the cornified layer becomes denuded, as occurs with extensive burns, the rate of evaporation can increase as much as 10-fold, to 3 to 5 L/day. For this reason, persons with burns must be given large amounts of fluid, usually intravenously, to balance fluid loss.

Insensible water loss through the respiratory tract normally averages about 300 to 400 ml/day. As air enters the respiratory tract, it becomes saturated with moisture to a vapor pressure of about 47 mm Hg before it is expelled. Because the vapor pressure of the inspired air is usually less than 47 mm Hg, water is continuously lost through the lungs with respiration. In cold weather, the atmospheric vapor pressure decreases to nearly 0, causing an even greater loss of water from the lungs as the temperature decreases. This process explains the dry feeling in the respiratory passages in cold weather.

Fluid Loss in Sweat. The amount of water lost by sweating is highly variable, depending on physical activity and environmental temperature. The volume of sweat normally is about 100 ml/day, but in very hot weather or during heavy exercise, fluid loss in sweat occasionally increases to 1 to 2 L/hour. This fluid loss would rapidly deplete the body fluids if intake were not also increased by activating the thirst mechanism, as discussed in Chapter 29.

Water Loss in Feces. Only a small amount of water (100 ml/day) normally is lost in the feces. This loss can increase to several liters a day in people with severe diarrhea. Therefore, severe diarrhea can be life-threatening if not corrected within a few days.

Water Loss by the Kidneys. The remaining water loss from the body occurs in the urine excreted by the kidneys. Multiple mechanisms control the rate of urine excretion.

Table 25-1 Daily Intake and Output of Water (ml/day)

Intake or Output	Normal	Prolonged Heavy Exercise
Intake		
Fluids ingested	2100	?
From metabolism	200	200
Total intake	2300	?
Output		
Insensible: skin	350	350
Insensible: lungs	350	650
Sweat	100	5000
Feces	100	100
Urine	1400	500
Total output	2300	6600

The most important means whereby the body maintains balance between water intake and output, as well as a balance between intake and output of most electrolytes in the body, is by controlling the rate at which the kidneys excrete these substances. For example, urine volume can be as low as 0.5 L/day in a dehydrated person or as high as 20 L/day in a person who has been drinking tremendous amounts of water.

This variability of intake is also true for most of the electrolytes of the body, such as sodium, chloride, and potassium. In some people, sodium intake may be as low as 20 mEq/day, whereas in others, sodium intake may be as high as 300 to 500 mEq/day. The kidneys have the task of adjusting the excretion rate of water and electrolytes to match the intake of these substances precisely, as well as compensating for excessive losses of fluids and electrolytes that occur in certain disease states. In Chapters 26 through 32, we discuss the mechanisms that allow the kidneys to perform these remarkable tasks.

BODY FLUID COMPARTMENTS

The total body fluid is distributed mainly between two compartments, the *extracellular fluid* and the *intracellular fluid* (**Figure 25-1**). The extracellular fluid is divided into the *interstitial fluid* and the blood *plasma*.

There is another small compartment of fluid that is referred to as *transcellular fluid*. This compartment includes fluid in the synovial, peritoneal, pericardial, and intraocular spaces, as well as the cerebrospinal fluid; it is usually considered to be a specialized type of extracellular fluid, although in some cases its composition may differ markedly from that of the plasma or interstitial fluid. All the transcellular fluids together constitute about 1 to 2 liters.

In a 70-kg adult man, the total body water is about 60% of the body weight, or about 42 liters. This percentage depends on age, sex, and degree of obesity. As a person grows older, the percentage of total body weight that is fluid gradually decreases. This decrease is due in part to

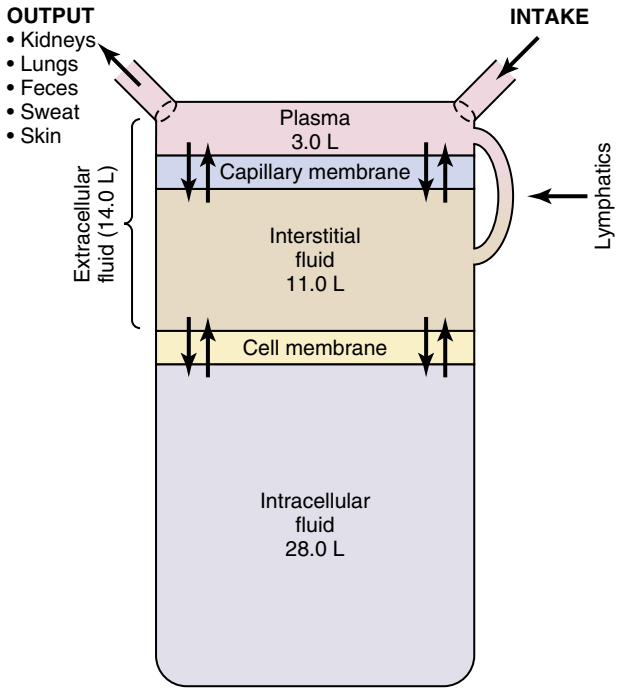

Figure 25-1. Summary of body fluid regulation, including the major body fluid compartments and the membranes that separate these compartments. The values shown are for an average 70-kg man.

the fact that aging is usually associated with an increased percentage of the body weight being fat, which decreases the percentage of water in the body.

Because women normally have a greater percentage of body fat compared with men, their total body water averages about 50% of the body weight. In premature and newborn babies, the total body water ranges from 70% to 75% of body weight. Therefore, when discussing average body fluid compartments, we should realize that variations exist depending on age, sex, and percentage of body fat.

In many other countries, the average body weight (and fat mass) has increased rapidly during the past 30 years. The average body weight for adult men older than 20 years in the United States is estimated to be approximately 88.8 kg (~196 pounds), and for adult women it is 77.4 kg (~170 pounds). Therefore, data discussed for an average 70-kg man in this and other chapters would need to be adjusted accordingly when considering body fluid compartments in most people.

INTRACELLULAR FLUID COMPARTMENT

About 28 of the 42 liters of fluid in the body are inside the trillions of cells and is collectively called the *intracellular fluid*. Thus, the intracellular fluid constitutes about 40% of the total body weight in an "average" person.

The fluid of each cell contains its individual mixture of different constituents, but the concentrations of these substances are similar from one cell to another. In fact, the composition of cell fluids is remarkably similar, even in different animals, ranging from the most primitive

microorganisms to humans. For this reason, the intracellular fluid of all the different cells together is considered to be one large fluid compartment.

EXTRACELLULAR FLUID COMPARTMENT

All the fluids outside the cells are collectively called the *extracellular fluid*. Together these fluids account for about 20% of the body weight, or about 14 liters in a 70-kg man. The two largest compartments of the extracellular fluid are the *interstitial fluid*, which makes up more than three-fourths (11 liters) of the extracellular fluid, and the *plasma*, which makes up almost one-fourth of the extracellular fluid, or about 3 liters. The plasma is the noncellular part of the blood; it exchanges substances continuously with the interstitial fluid through the pores of the capillary membranes. These pores are highly permeable to almost all solutes in the extracellular fluid except the proteins. Therefore, the extracellular fluids are constantly mixing, so the plasma and interstitial fluids have about the same composition, except for proteins, which have a higher concentration in the plasma.

BLOOD VOLUME

Blood contains extracellular fluid (the fluid in plasma) and intracellular fluid (the fluid in the red blood cells). However, blood is considered to be a separate fluid compartment because it is contained in a chamber of its own—the circulatory system. The blood volume is especially important in the control of cardiovascular dynamics.

The average blood volume of adults is about 7% of body weight, or about 5 liters. About 60% of the blood is plasma and 40% is red blood cells, but these percentages can vary considerably in different people, depending on sex, weight, and other factors.

Hematocrit (Packed Red Blood Cell Volume). The hematocrit is the fraction of the blood composed of red blood cells, as determined by centrifuging blood in a hematocrit tube until the cells become tightly packed in the bottom of the tube. Because the centrifuge does not completely pack the red blood cells together, about 3% to 4% of the plasma remains entrapped among the cells, and the true hematocrit is only about 96% of the measured hematocrit.

In men, the measured hematocrit is normally about 0.40, and in women, it is about 0.36. In persons with severe *anemia*, the hematocrit may fall as low as 0.10, a value that is barely sufficient to sustain life. Conversely, in persons with some conditions, excessive production of red blood cells occurs, resulting in *polycythemia*. In these persons, the hematocrit can rise to 0.65.

CONSTITUENTS OF EXTRACELLULAR AND INTRACELLULAR FLUIDS

Comparisons of the composition of the extracellular fluid, including the plasma and interstitial fluid, and the intracellular fluid are shown in **Figures 25-2** and **25-3** and in **Table 25-2**.

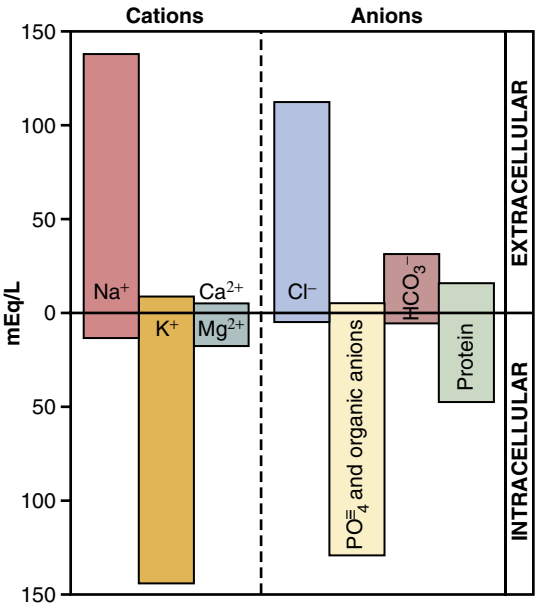

Figure 25-2. Major cations and anions of the intracellular and extracellular fluids. The concentrations of Ca^{2+} and Mg^{2+} represent the sum of these two ions. The concentrations shown represent the total of free ions and complexed ions.

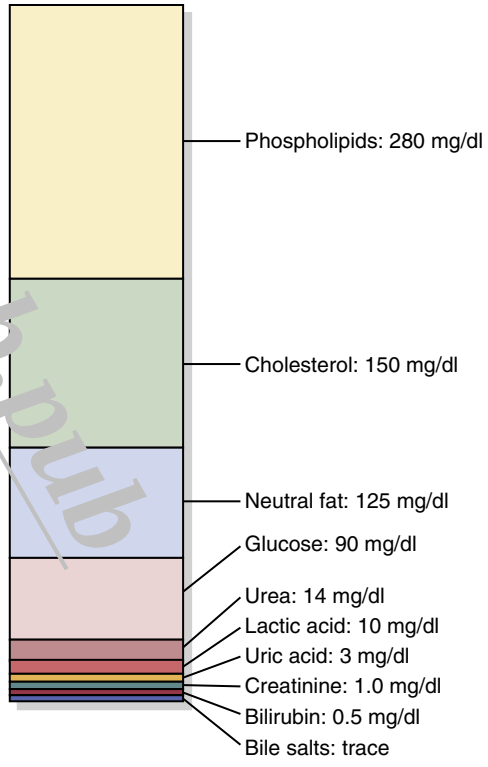

Figure 25-3. Nonelectrolytes of the plasma.

Similar Ionic Composition of Plasma and Interstitial Fluid

Because the plasma and interstitial fluid are separated only by highly permeable capillary membranes, their

Table 25-2 Osmolar Substances in Extracellular and Intracellular Fluids

Substance	Plasma (mOsm/L H_2O)	Interstitial (mOsm/L H_2O)	Intracellular (mOsm/L H_2O)
Na^+	142	139	14
K^+	4.2	4.0	140
Ca^{2+}	1.3	1.2	0
Mg^{2+}	0.8	0.7	20
Cl^-	106	108	4
HCO_3^-	24	28.3	10
HPO_4^-, $H_2PO_4^-$	2	2	11
SO_4^-	0.5	0.5	1
Phosphocreatine			45
Carnosine			14
Amino acids	2	2	8
Creatine	0.2	0.2	9
Lactate	1.2	1.2	1.5
Adenosine triphosphate			5
Hexose monophosphate			3.7
Glucose	5.6	5.6	
Protein	1.2	0.2	4
Urea	4	4	4
Others	4.8	3.9	10
Total mOsm/L	299.8	300.8	301.2
Corrected osmolar activity (mOsm/L)	282.0	281.0	281.0
Total osmotic pressure at 37°C (98.6°F) (mm Hg)	5441	5423	5423

ionic composition is similar. The most important difference between these two compartments is the higher concentration of protein in the plasma; because the capillaries have a low permeability to the plasma proteins, only small amounts of proteins are leaked into the interstitial spaces in most tissues.

Because of the *Donnan effect*, the concentration of positively charged ions (cations) is slightly greater (~2%) in plasma than in interstitial fluid. Plasma proteins have a net negative charge and therefore tend to bind cations such as sodium and potassium ions, thus holding extra amounts of these cations in the plasma, along with the plasma proteins. Conversely, negatively charged ions (anions) tend to have a slightly higher concentration in interstitial fluid compared with plasma because the negative charges of the plasma proteins repel the negatively charged anions. For practical purposes, however, the concentrations of ions in interstitial fluid and plasma are considered to be about equal.

Referring again to **Figure 25-2**, one can see that the extracellular fluid, including the plasma and interstitial fluid, contains large amounts of sodium and chloride ions and reasonably large amounts of bicarbonate ions but only small quantities of potassium, calcium, magnesium, phosphate, and organic acid ions. The composition of extracellular fluid is carefully regulated by various mechanisms, but especially by the kidneys, as discussed later. This regulation allows the cells to remain continually bathed in a fluid that contains the proper concentration of electrolytes and nutrients for optimal cell function.

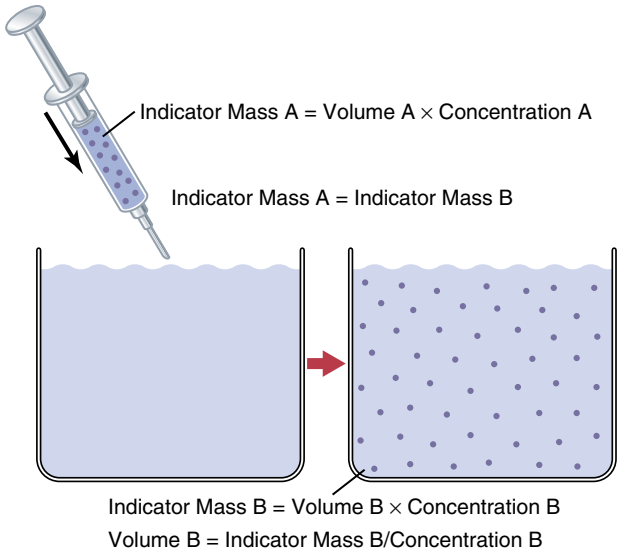

Figure 25-4. Indicator-dilution method for measuring fluid volumes.

INTRACELLULAR FLUID CONSTITUENTS

The intracellular fluid is separated from the extracellular fluid by a cell membrane that is highly permeable to water but is not permeable to most electrolytes in the body. In contrast to the extracellular fluid, the intracellular fluid contains only small quantities of sodium and chloride ions and almost no calcium ions. Instead, it contains large amounts of potassium and phosphate ions plus moderate quantities of magnesium and sulfate ions, all of which have low concentrations in the extracellular fluid. Also, cells contain large amounts of protein—almost four times as much as in the plasma.

MEASUREMENT OF BODY FLUID COMPARTMENT VOLUMES—INDICATOR-DILUTION PRINCIPLE

The volume of a fluid compartment in the body can be measured by placing an indicator substance in the compartment, allowing it to disperse evenly throughout the compartment's fluid, and then analyzing the extent to which the substance becomes diluted. **Figure 25-4** shows this *indicator-dilution method* of measuring the volume of a fluid compartment. This method is based on the conservation of mass principle, which means that the total mass of a substance after dispersion in the fluid

compartment will be the same as the total mass injected into the compartment.

In the example shown in Figure 25-4, a small amount of dye or other substance contained in the syringe is injected into a chamber, and the substance is allowed to disperse throughout the chamber until it becomes mixed in equal concentrations in all areas. Then a sample of fluid containing the dispersed substance is removed, and the concentration is analyzed chemically, photoelectrically, or by other means. If none of the substance leaks out of the compartment, the total mass of substance in the compartment (Volume B × Concentration B) will equal the total mass of the substance injected (Volume A × Concentration A). By simple rearrangement of the equation, one can calculate the unknown volume of chamber B as follows:

$$\text{Volume B} = \frac{\text{Volume A} \times \text{Concentration A}}{\text{Concentration B}}$$

For this calculation, one needs to know the following: (1) the total amount of substance injected into the chamber (the numerator of the equation); and (2) the concentration of the fluid in the chamber after the substance has been dispersed (the denominator).

For example, if 1 milliliter of a solution containing 10 mg/ml of dye is dispersed into chamber B, and the final concentration in the chamber is 0.01 mg/ml of fluid, the unknown volume of the chamber can be calculated as follows:

$$\text{Volume B} = \frac{1\,\text{ml} \times 10\,\text{mg/ml}}{0.01\,\text{mg/ml}} = 1000\,\text{ml}$$

This method can be used to measure the volume of virtually any compartment in the body as long as the following occur: (1) the indicator disperses *evenly* throughout the compartment; (2) the indicator disperses *only* in the compartment that is being measured; and (3) the indicator is *not metabolized or excreted*. If the indicator is metabolized or excreted, correction must be made for loss of the indicator from the body. Several substances can be used to measure the volume of each of the different body fluids.

DETERMINATION OF VOLUMES OF SPECIFIC BODY FLUID COMPARTMENTS

Measurement of Total Body Water. Radioactive water (tritium, ^3H_2O) or heavy water (deuterium, ^2H_2O) can be used to measure total body water. These forms of water mix with the total body water within a few hours after being injected into the blood, and the dilution principle can be used to calculate total body water (Table 25-3). Another substance that has been used to measure total body water is *antipyrine*, which is very lipid-soluble, rapidly penetrates cell membranes, and distributes uniformly throughout the intracellular and extracellular compartments.

Table 25-3 Measurement of Body Fluid Volumes

Volume	Indicators
Total body water	^3H_2O, ^2H_2O, antipyrine
Extracellular fluid	^{22}Na, ^{125}I-iothalamate, thiosulfate, inulin
Intracellular fluid	(Calculated as total body water—extracellular fluid volume)
Plasma volume	^{125}I-albumin, Evans blue dye (T-1824)
Blood volume	^{51}Cr-labeled red blood cells, or calculated as blood volume = plasma volume/(1 – hematocrit)
Interstitial fluid	Calculated as extracellular fluid volume – plasma volume

Measurement of Extracellular Fluid Volume. The volume of extracellular fluid can be estimated using any of several substances that disperse in the plasma and interstitial fluid but do not readily permeate the cell membrane. These include radioactive sodium, radioactive chloride, radioactive iothalamate, thiosulfate ion, and inulin. When any one of these substances is injected into the blood, it usually disperses almost completely throughout the extracellular fluid within 30 to 60 minutes. Some of these substances, however, such as radioactive sodium, may diffuse into the cells in small amounts. Therefore, one frequently speaks of the *sodium space* or *inulin space* instead of calling the measurement the true extracellular fluid volume.

Calculation of Intracellular Volume. The intracellular volume cannot be measured directly. However, it can be calculated as follows:

Intracellular volume
= Today body water – Extracellular volume

Measurement of Plasma Volume. Plasma volume can be measured using a substance that does not readily penetrate capillary membranes but remains in the vascular system after injection. One of the most commonly used substances for measuring plasma volume is serum albumin labeled with radioactive iodine (^{125}I-albumin) or with a dye that avidly binds to the plasma proteins, such as *Evans blue dye* (also called *T-1824*).

Calculation of Interstitial Fluid Volume. Interstitial fluid volume cannot be measured directly, but it can be calculated as follows:

Interstitial fluid volume
= Extracellular fluid volume – Plasma volume

Measurement of Blood Volume. If one measures the *hematocrit* (the fraction of the total blood volume composed of cells) and plasma volume using the methods described earlier, blood volume can also be calculated using the following equation:

$$\text{Total blood volume} = \frac{\text{Plasma volume}}{1 - \text{Hematocrit}}$$