9

The Biological Disposition of Drugs and Inorganic Toxins

Introduction

This chapter is a discussion of how some foreign substances get into the body, how they become distributed, what their effects are, and how they are eliminated from the body. Lead is the exemplar in the biological discussion, but the biological concepts can be applied to many other substances. The mathematical discussion focuses on lead poisoning and on pharmaceuticals.

Lead can be eaten, inhaled, or absorbed through the skin; it is then distributed to other tissues by the blood. Some of it is then removed from the body by excretion and defecation. Any lead that is retained in the body can have unpleasant biological consequences—anemia and mental retardation, for instance. These processes can be understood only at the levels of organ systems and of the tissues that make up those organs. Thus this chapter includes discussions of the lungs, the digestive tract, the skin, blood, the circulatory system, bones, and the kidneys, all of which are involved in the effects of lead on humans.

9.1 The Biological Importance of Lead

No biological requirement for lead has ever been demonstrated. Rather, there is much experimental evidence that it is toxic. Lead is sparsely distributed in nature, but mining activities to support the manufacture of batteries, leaded gasoline, and other products have concentrated it.

Trace metals play an important role in nutrition.

A number of metallic elements play crucial roles in our nutrition, usually in small amounts. Sodium is necessary to nerve conduction, iron is an essential part of hemoglobin, and magnesium is a component of chlorophyll. In many cases, traces of metals are required for the correct functioning of biomolecules; examples are copper, manganese, magnesium, zinc, and iron. On the other hand, no human metabolic

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need for lead has ever been demonstrated, whereas the toxic effects of lead are well documented.

Most lead enters the biosphere through human-made sources.

Lead is found in the earth's crust in several kinds of ore. Its natural concentration in any one place is almost always quite low and is of little concern to biology. Commercial uses for lead, however, have produced locally high concentrations of the metal in air, water, and soil (see [1] and [2]).

About 40% of the refined lead in the Western world is used in the manufacture of batteries, and another 10% finds its way into antiknock compounds in gasoline. Cable sheathing and pipes account for about another 15%. Still more is used in paints, glassware, ceramics, and plastics. Fortunately, the use of lead in interior paints and gasoline has lately been approaching zero in the USA and some other countries.

A biological compartment model shows the paths of lead into, around, and out of an organism.

It often happens that a particular material, introduced into one part of an organism, quickly reaches a common concentration in several other parts of the organism. The various parts in which this equilibration occurs constitute a single *biological compartment*. Note that the parts of a compartment can be organ systems, organs, or parts of an organ, and that they need not be near each other if a suitable distribution system is available (see [3]).

Figure 9.1.1 illustrates these concepts in a biological compartment model for lead. One compartment is the blood, in which flow and turbulence cause rapid mixing. The blood carries the lead to "soft tissues," which we take to mean all tissues that are neither bone nor blood. All these soft tissues behave similarly toward lead and take it up to about the same degree, so they can be considered to constitute a second compartment.[1] A third compartment is bone, in which lead has a very long half-life. The fourth compartment is implied: It is the environment, from which the lead originates and to which it must ultimately return, either through living biological processes or at the death of the organism. The arrows connecting the compartments show the direction of lead movement between the various compartments.

9.2 Early Embryogenesis and Organ Formation

In discussions of the uptake and metabolism of toxins and drugs, the relevant compartments are almost always organs and groups of organs. This section presents some information about how organs develop in embryos. We show that organs and

[1] This is a somewhat rough approximation: The aorta, the main artery out of the heart, is a soft tissue that seems not to equilibrate lead quickly with other soft tissues. Further, the behavior of a few other soft tissues toward lead seems to depend on the national origin and age of the cadavers used in the data collection. (See Schroeder and Tipton [4].)

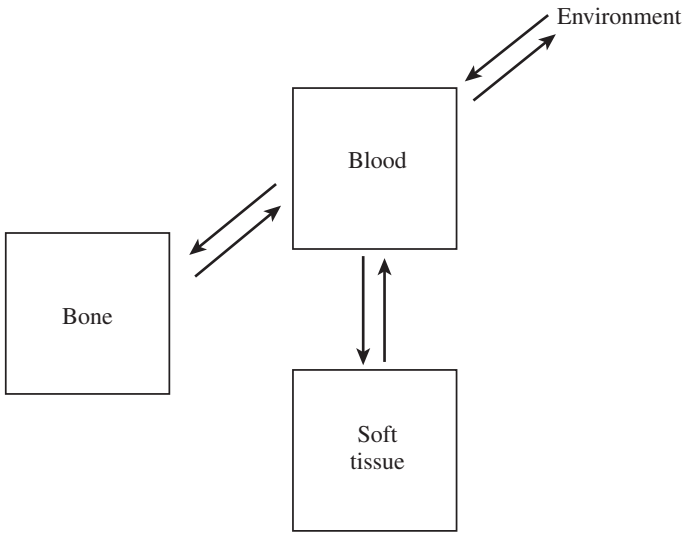


Fig. 9.1.1. A compartment model of the three biological tissue types among which lead becomes distributed, and the relationship of the compartments to the environmental compartment.

their interdependence on one another develop from the very start. This will allow us to treat organs as a group of interacting compartments for mathematical purposes. Thus the stage will be set for our discussion of lead poisoning.

Specific organs have evolved in multicellular organisms to perform very specific biological tasks. This functional specialization has a benefit and a cost. The benefit is that a given organ is usually very efficient at performing its assigned biological tasks. The cost is that the organ generally can do little else and must therefore rely on other organs to support it in other functions. As examples, the heart is a reliable blood pump and the kidneys efficiently remove nitrogenous wastes from blood. However, the heart is dependent on the kidneys to remove blood wastes that would be detrimental to the heart, and the kidneys are dependent on the heart to pump blood at a high enough pressure to make the kidneys work.

Early divisions of fertilized eggs result in an unchanged total cell mass.

A fertilized egg, or *zygote*, starts to divide by mitosis soon after fertilization. In the case of humans, this means that division starts while the zygote is still in the oviduct. Early divisions merely result in twice the number of cells, without any increase in total cell mass, and are thus called *cleavage divisions* (see [5]).

A one-celled zygote contains the full complement of genes available to the organism.[2] As mitosis proceeds, many of the new cells *differentiate*, or take up more specialized functions, a process that coincides with the inactivation of unneeded

[2] In Chapter 10, we will discuss an exception to this statement: Certain viruses can insert genes into cells.

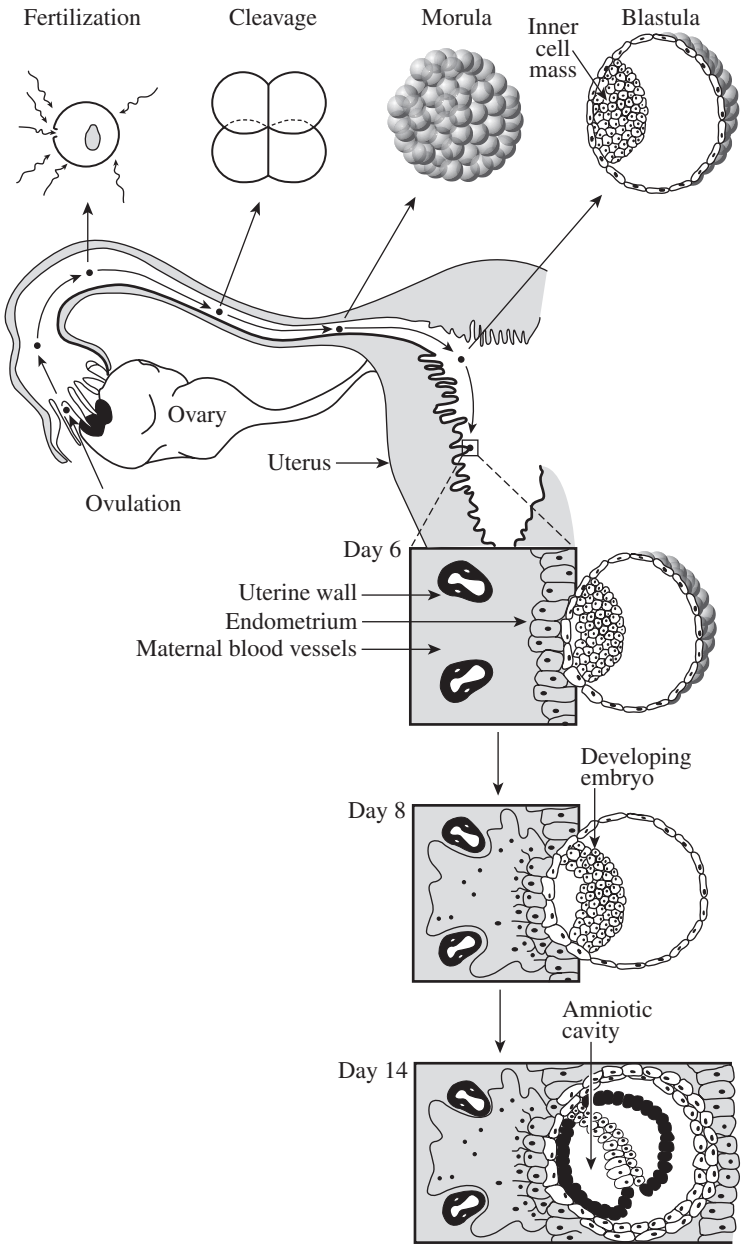


Fig. 9.2.1. The stages of development of a mammalian fetus, arranged with respect to where they occur in the female reproductive system. A single cell becomes a mass of cells (called a morula) and then forms a hollow ball (a blastula), with the inner cell mass at one side. (Redrawn from W. Purves, G. Orians, and C. Heller, *Life: The Science of Biology*, 4th ed., Sinauer Associates, Sunderland, MA, 1995. Used with permission.)

genes. The genes that remain active in a particular cell are those that determine the functional nature of that cell. Thus cells of the heart and of the liver require different sets of active genes (although the two sets certainly overlap).[3] The gene inactivation process starts early: Even before the heart organ itself becomes obvious, there are heart precursor cells that individually contract. Soon, however, a functioning heart and blood vessels develop in concert with the fetus's need for a continuing blood supply.

Higher organisms have a three-layer body plan.

Embryos of each species have their own unique behavior, but there are several events in embryogeny that are shared among most multicellular species: Early cleavage generates a solid mass of cells, which then hollows out. Next, cell proliferation and movement create three basic tissue layers. Finally, the various organ systems develop out of these basic tissue layers. We will follow a human zygote through these steps.

Fertilization of the human egg occurs in the upper third of the oviduct, after which the zygote moves toward the *uterus*, a powerful muscular organ (see Figure 9.2.1). The initial cleavage divisions take place in the oviduct, and result in a solid ball of cells that resembles a mulberry; its name, *morula*, is taken from the Latin word for that fruit. The morula hollows out to form the structure shown in Figure 9.2.1. It is called a *blastocyst* and consists of an outer sphere of cells, with an inner cell mass at one end. When the blastocyst reaches the uterus, it embeds into the uterine wall, a process called *implantation*, at about day 8.

Figures 9.2.2 and 9.2.3 illustrate embryonic development after implantation. To start, the embryo is little more than a disk of cells, but an elongated structure called the *primitive streak* soon forms along what will be the head-to-foot axis. Cells on the outer margins of the primitive streak migrate toward it, downward through it, and into the interior of the disk of cells. (Figure 9.2.2 is a perspective view and Figure 9.2.3 is a cross-section through the disk.) This migration, called *gastrulation*, establishes three *germ layers* of tissue from which all subsequent organs will develop. These germ layers are the *endoderm*, the *mesoderm*, and the *ectoderm*. Next, the tips of the embryo fold down and around, a process that establishes the tubular nature of the embryo (Figure 9.2.3(c)). The endoderm will form much of the digestive tract and lungs, the ectoderm will form the skin and nervous system, and the mesoderm, lying in between the other two layers, will form many of the internal organs. Figure 9.2.3(c) is a cross-section of the fetus, which projects outward from the plane of the diagram.

The placenta is the interface between mother and fetus.

Mammalian fetuses are suspended in a watery *amniotic fluid* in a membranous sac

[3] Inactivation of unneeded genes by a cell is a common event. For example, different genes are active in different parts of a single division cycle. Even the inactivation of embryonic genes during early development is not irreversible: Crabs can grow new claws, plant stems can be induced to grow roots, and the genes for cell division are reactivated in cancer cells.

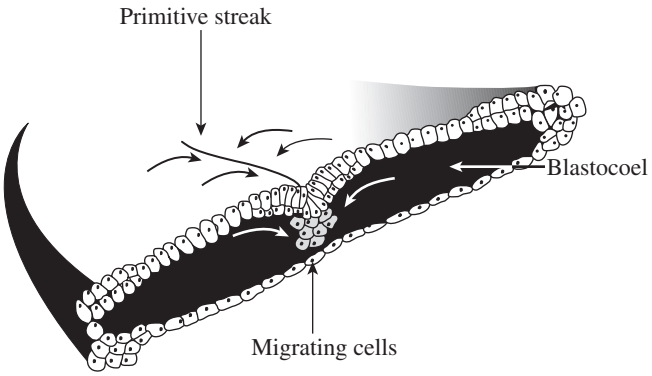


Fig. 9.2.2. A perspective view of gastrulation. Cells move from the sides, into the primitive streak, and downward into the embryo. (Redrawn from W. Purves, G. Orians, and C. Heller, *Life: The Science of Biology*, 4th ed., Sinauer Associates, Sunderland, MA, 1995. Used with permission.)

called the *amnion*; this structure cushions the fetus against mechanical injury.[4] As pointed out in Chapter 6, the blood of the mother and her fetus do not mix, a fact that necessitates a special structure for the exchange of maternal and fetal materials: A flat, platelike organ called the *placenta* develops between mother and child at the point of implantation; recall the discussion in Section 6.3. All materials exchanged between mother and child cross at the placenta, one side of which is composed of fetal tissues and the other side of which is composed of maternal uterine tissue. The two sides of the placenta have interdigitating projections into each other to increase their area of contact, thus facilitating material exchange. Lead is among the many substances that cross the placenta; thus a mother can poison her fetus by passing lead to it.

Shortly after it leaves the fetal heart, the fetus's blood is shunted outward into a vessel in the *umbilical cord* and into the placenta. At the placenta the fetal blood takes O_2 and nutrients from the mother's blood and gives up CO_2 and wastes. The fetus's blood, after having been enriched in O_2 and nutrients and cleansed of CO_2 and wastes, returns to the fetal body through the umbilical cord.

The evolutionary development of the coelom facilitated the evolution of large animals.

During embryogenesis in the higher animals, a cavity forms in the center of the mesoderm (Figure 9.2.3). This cavity is the *coelom*, and it has played a major role in the evolution of large animals (larger than $\approx$ 1 cm). By definition, a body cavity is called a coelom only if it is completely surrounded by mesoderm, the latter being identified by its creation during gastrulation and its role in forming specific internal organs, e.g., bones, muscles, heart, sex organs, and kidneys.

[4] An amnion and amniotic fluid are also found in the eggs of egg-laying mammals and reptiles and in bird eggs.

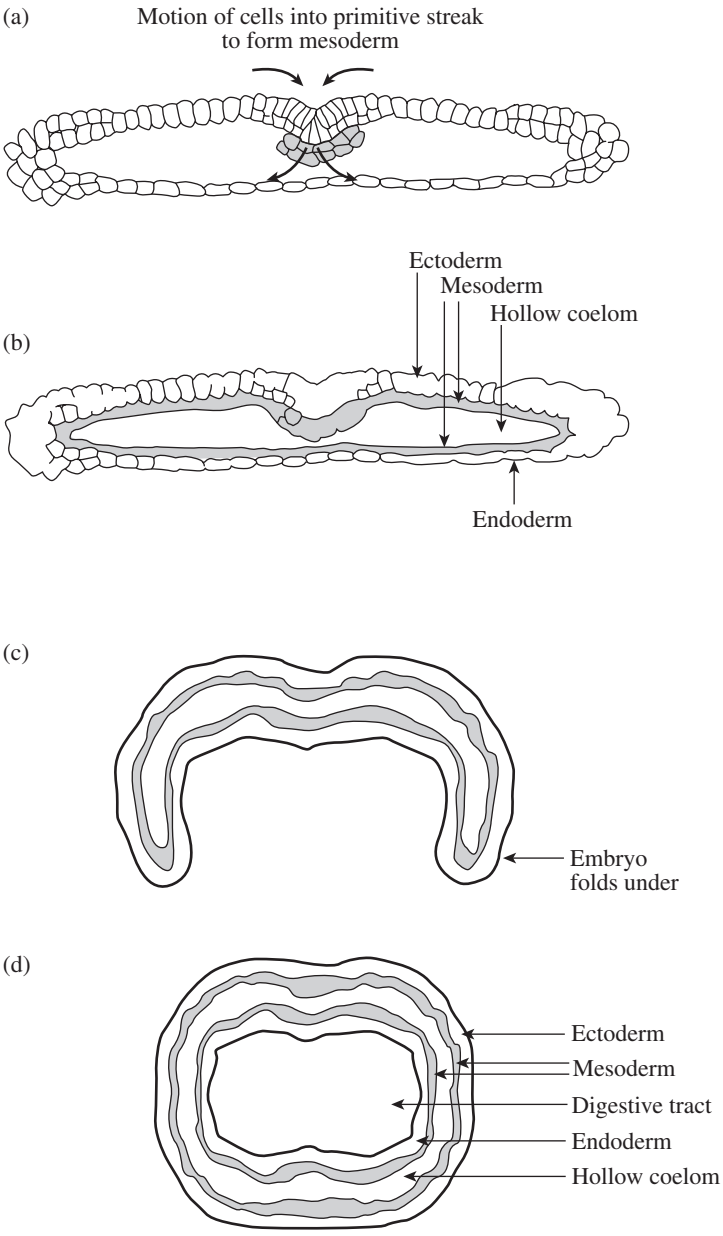


Fig. 9.2.3. A cutaway view of gastrulation, showing how the mesodermal layer defines the coelom. All the structures shown project out of the plane of the paper. (a) The cells move toward the primitive streak, then down into the interior of the zygote. (b) These cells form the mesodermal lining of the coelom. (c) This process is followed by a curling of the embryo to form the digestive tract. (d) This is a cross-section of the elongated fetus. It forms a tube, with the digestive tract running down the center.

A coelom provides room for the seasonal enlargement of the reproductive systems of some animals, notably birds. In addition, a coelom separates the muscles of the digestive tract from those of the body wall, allowing the two to function independently of one another. For purposes of our discussion of lead poisoning, however, a coelom plays two roles (to be described at length below): First, a coelom provides room into which the lungs can expand during breathing. Second, a coelom is important in determining the structural properties of the circulatory system: Large animals require a powerful heart, one that can expand and contract appreciably. A coelomic cavity provides space for a beating heart to change its size.

9.3 Gas Exchange

The lungs are gas exchange organs. This means, however, that they can provide an efficient entry route into our bodies for foreign substances such as lead. For example, the air we breathe may contain lead from leaded gasoline and particulate lead, mainly from lead smelters. About 40% *of the lead we inhale is absorbed into the blood from the lungs. In this section, we discuss the anatomy and functioning of our lungs.*

Animals can exchange gas with the outside world.

Gas exchange between an animal and the atmosphere is diffusion controlled. Thus two physical factors influence the rate at which an animal gives up CO_2 and takes up O_2 across membranes from its surroundings—these factors are concentration gradients and surface area; recall (6.2.13). The concentration gradients are provided naturally by the metabolic use of O_2 and the subsequent production of CO_2 in respiring tissues. Carbon dioxide–rich/oxygen-poor blood arrives at an animal's gas exchange organs, where passive diffusion causes CO_2 to move outward to the environment and O_2 to move inward from the environment (Figure 9.3.1).

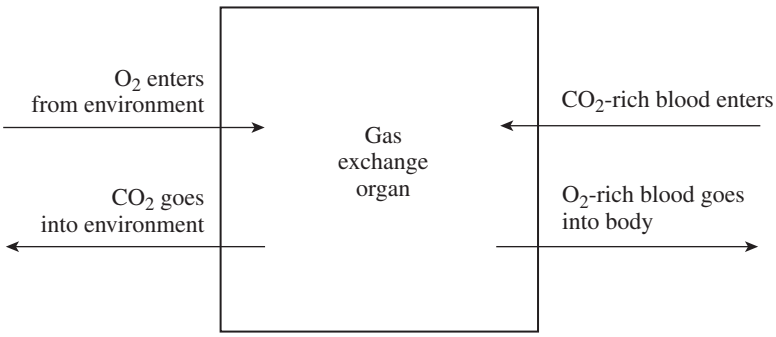


Fig. 9.3.1. A gas exchange organ. Blood with an excess of CO_2 and a deficiency of O_2 arrives at the gas exchange organ. Concentration gradients drive CO_2 from the blood into the atmosphere and O_2 from the atmosphere into the blood.

Several organs other than lungs can serve as sites of gas exchange: In insects, tiny *tracheal tubes* carry air directly to and from target tissues. The skin of some animals, notably amphibians, is a gas exchange organ. Many aquatic animals have *gills*, which are feathery structures that contain networks of blood vessels over which water can flow. The water brings in O_2 and carries away CO_2. We are most concerned, however, with humans, which, along with all other mammals and birds, exchange gases in *lungs* (see [6] and [7]).

Lungs themselves have no muscles, and are therefore incapable of pumping air in and out. Instead, air is pushed in and out of the lungs indirectly: Inhalation occurs when a set of *intercostal* muscles moves the ribs so as to increase the front-to-back size of the chest cavity (i.e., the coelom). At the same time, a dome-shaped sheet of muscle (the *diaphragm*) at the base of the chest cavity contracts and moves downward (Figure 9.3.2). The two actions expand the volume of the chest cavity and thereby draw air into the lungs. On the other hand, exhalation occurs when those intercostal muscles and the diaphragm relax.[5]

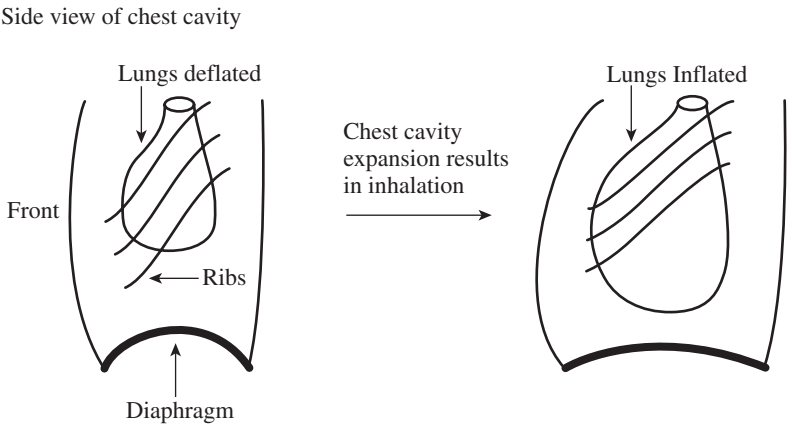


Fig. 9.3.2. The process of inhalation. The lungs have no muscles of their own. Their expansion and contraction are driven by the expansion and contraction of the chest cavity. Exhalation can also occur if the person simply relaxes, allowing the chest cavity to become smaller.

Air enters the lungs through tubes that branch out profusely, and which lead to small sacs called *alveoli*. It is the large number of alveoli that gives the lungs their extensive surface exposure to the outside world—about 100 m^2 of area. The alveoli are lined with tiny blood vessels that exchange CO_2 and O_2 with the atmosphere, giving up CO_2 to the environment and then carrying O_2 to tissues.

[5] Forcible exhalation of air does not result from the reverse action of the muscles mentioned for inhalation. Muscles can exert force only in contraction, and thus a second set of intercostal muscles and certain abdominal muscles act to push air forcibly from the lungs by moving the front of the ribs *downward* and decreasing the volume of the chest cavity.

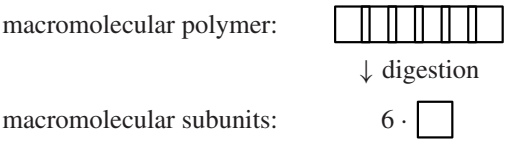
9.4 The Digestive System

This section is a discussion of the function of our digestive tract, a system of organs uniquely able to take nutrient materials, as well as toxins like lead, from our environment and route them into our blood.

The digestive system is an important path for lead intake. Rain washes atmospheric lead into municipal water supplies and people drink it. Lead in the pipes and solder of home water distribution systems leaches into drinking water.[6] *Wine may have a high lead content. Plants absorb lead through their roots or bear it on their surfaces; the plants may then be consumed by humans. Organ meats, particularly kidneys, may contain high lead concentrations. Children may eat lead-based paint from old furniture. The fraction of ingested lead that is absorbed by the digestive tract is usually about* 10–15% *but may approach* 45% *during fasting* (*perhaps because it does not compete with food for absorption*).

Digestion is the splitting of biopolymers into smaller pieces.

The word "digestion" has a very restricted meaning in physiology: It is a particular way of splitting the linkage between the components in a macromolecular polymer. The process is modeled thus:



Recall our discussion of macromolecular structure in Chapter 8. When we eat a large molecule, the process of digestion breaks it into smaller molecules. These smaller molecules are then either metabolized further to extract energy or are used to make building blocks for our own macromolecules (see [6] and [7]).

The mammalian digestive tract is a series of specialized organs.

At a fairly early stage in the evolution of animals, different parts of the digestive tract assumed different roles. In particular, the various organs of the digestive system reflect the animal's lifestyle. Figure 9.4.1 is a diagram of a mammalian digestive system; we will use it for the ensuing discussion.

(a) *Dentition*. Teeth are used for cutting, piercing, and grinding. Extreme development of the piercing teeth is typical of predators; cutting and grinding teeth are prominent in herbivores. Human dentition is more characteristic of herbivores than of carnivores.

[6] Lead is poorly soluble in water unless oxygen is present, a condition unfortunately met in most drinking water.

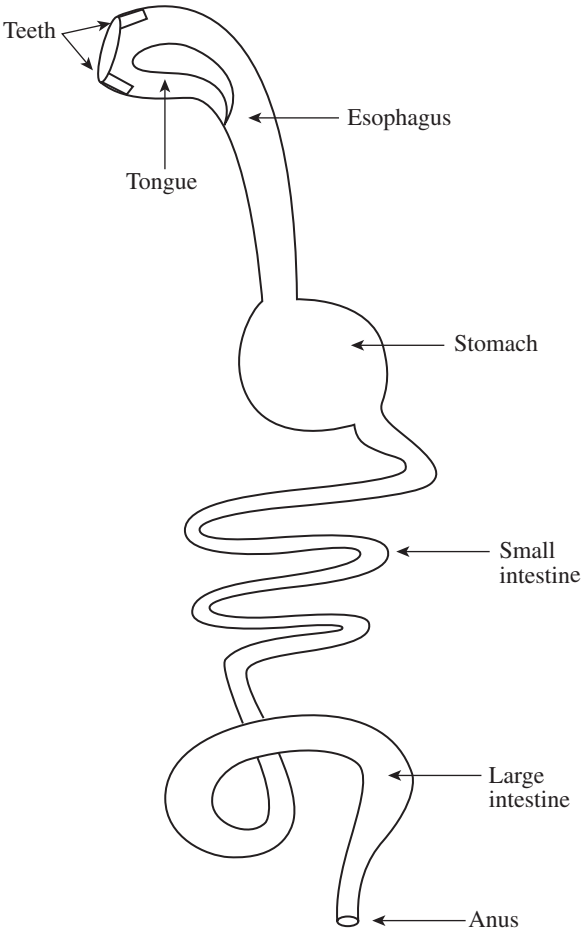


Fig. 9.4.1. The digestive tract is a convoluted tube, with different portions performing different specialized functions. See text for details.

(b) *Tongue*. This organ pushes food back into the esophagus, which leads to the stomach. The act of swallowing pushes a small flap over the opening to the windpipe, or *trachea*, which minimizes the possibility of choking on food.

(c) *Esophagus*. This is the tube leading from the back of the mouth cavity to the stomach.

(d) *Stomach*. This is an organ of mixing and, to a lesser extent, digestion; except for small molecules such as water and ethanol, very little absorption takes place from the stomach into the blood. The presence of food in the stomach triggers the process of digestion: Glands in the wall of the stomach generate hydrochloric acid, which contributes directly to the chemical breakup of food and creates the

acidic environment required by other digestive agents. (These agents are called *enzymes*; they were discussed in detail in Chapter 8.)

Stomach muscles churn the food and the stomach secretions to mix them. In our earlier discussion, it was pointed out that the coelom separates the voluntary muscles of the outer body from the involuntary muscles of the digestive tract and allows them to work independently of each other. Thus the involuntary movements of the digestive tract (called *peristalsis*) relieve us of the need to walk around waving our arms and wiggling in order to move food along our digestive tract.

(e) *Small intestine*. Peristalsis moves the food along and mixes it with a large variety of digestive enzymes from the pancreas and from the small intestine itself. Surprisingly, these enzymes function only near neutral pH, which is attained by the secretion of alkali ions from the pancreas to neutralize stomach acid.

The lining of the small intestine has a very large surface area, generated in several ways. First, the small intestine is very long, especially in herbivores. (Plant matter contains a great deal of a carbohydrate called *cellulose*, which is very difficult to digest, so plant-eaters need a long intestine.) Second, there are the numerous intestinal folds, called *villi*. Third, each cell in the intestinal lining has hundreds of small projections, called *microvilli*. The total absorptive surface of the human small intestine is several hundred square meters!

Most absorption of digested food takes place in the small intestine. Molecular subunits of carbohydrates (e.g., starch and sugars), proteins (e.g., meat) and fats are absorbed throughout the highly convoluted intestinal surface and into the blood.

(f) *Large intestine*. Undigested matter and water collect in the large intestine, also called the *colon*. Most of the water is pumped out into the blood, leaving the waste, called *fecal matter*, which is expelled through the *anus*. Ingested lead, if not absorbed in the digestive tract, is removed from the body in fecal matter.

9.5 The Skin

The third pathway by which chemicals can enter our bodies is through the skin. We will examine the unique properties of our skin and the conditions under which lead can cross it.

Skin is a sensor of, and a waterproof barrier to, the outside world.

Skin is uniquely constructed to be the interface to our environment. Working from the inside to the outside of our skin, there is first a layer rich in small blood vessels, or *capillaries*. Capillaries bring nutrients and oxygen to the skin to support the needs of the many nearby nerve endings and other specialized cells that detect stimuli such as pain, pressure, and heat.

The next skin layer, also requiring materials brought by the blood, is a group of rapidly dividing, pancake-shaped cells. As these cells divide, they push toward the outside and die. The final, outer skin layer, called the *stratum corneum*, consists of these dead cells. Thus we are surrounded by a layer of dead cells, of which the membranes are a principal remnant. It is this layer that we need to examine more closely in our discussion of lead poisoning.

Cellular membranes were described in Chapter 6; we can review that discussion by pointing out that the principal structural components of cell membranes are closely related to fats. Thus cell membranes are waterproof, a property that makes good sense. After all, most biological chemistry is water-based, and therefore we need to protect our interior aqueous environment from our exterior environment, which is also mostly aqueous.

There are, however, chemicals that can penetrate the cell membranes of the stratum corneum and other cells and thereby get into our bloodstreams. Because membranes contain a lot of fatlike molecules, we should not be surprised that some fat-soluble compounds may move across membranes via a temporary state in which the substances become transiently dissolved in the membrane. Absorption of compounds across the skin is said to be *percutaneous*.[7] Examples of such compounds are tetramethyl lead and tetraethyl lead, "antiknock" compounds found in leaded gasoline. It was common in days past to see people hand-washing machine parts in leaded gasoline, an activity virtually guaranteed to cause lead absorption.

9.6 The Circulatory System

Our circulatory system partitions chemicals throughout the body. It picks them up at the lungs, the digestive tract, and the skin and distributes them to other body tissues. In the case of lead poisoning, the circulatory system plays another key role: One of the most important toxic effects of lead is to interfere with the synthesis of the oxygen-carrying pigment hemoglobin, found in red blood cells. We will describe the circulatory system and show how its anatomy promotes the rapid distribution of materials to all other body tissues.

The discussion of oxygen transfer across the placenta in Section 6.3 *was a short introduction to some of the material in this section.*

Circulatory systems move a variety of materials around an animal's body.

Living organisms are open thermodynamic systems, which means that they are constantly exchanging energy and matter with their surroundings. The exchange of materials between the cells of a multicellular animal and the animal's environment

[7] The compound dimethylsulfoxide (DMSO) rapidly penetrates the skin and is sold as a remedy for certain bone joint disorders. It is possible to taste DMSO by sticking one's finger into it: The compound crosses the skin of the finger, gets into the bloodstream, and goes to the tongue, where it generates the sensation of taste—said variously to be like garlic or oysters.

is mediated by a circulatory system. This system picks up O_2 at the lungs, gills, tracheal tubes, or skin, and delivers it to metabolizing cells. The CO_2 that results from the metabolic production of energy is returned to the gas exchange organ and thus to the organism's surroundings. The circulatory system also picks up nutrients at the digestive tract and delivers them to the body's cells; there it picks up wastes, which it takes to the kidneys or related organs for excretion. Further, the blood carries minerals, proteins, and chemical communicators, or *hormones*, from one part of the body to the other. Hormones regulate such activities as growth, digestion, mineral balances, and metabolic rate (see [6] and [7]).

Open circulatory systems are convenient, but inefficient.

The blood of most small invertebrate animals spends most of its time circulating leisurely around the animal's internal organs. An example is shown in Figure 9.6.1. Note that the blood is not necessarily confined to vessels at all; rather, it merely bathes the internal organs. This kind of circulatory system is said to be *open*.

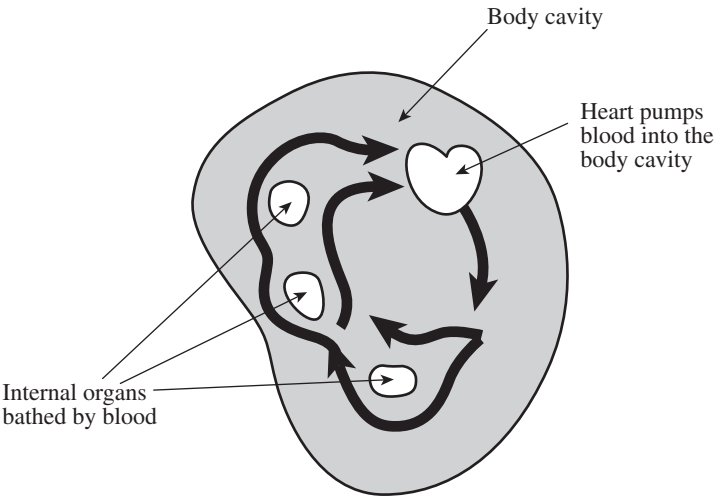


Fig. 9.6.1. An open circulatory system. The heart pumps blood into an open body cavity. Organs in the body cavity are bathed by the blood, exchanging gases, nutrients, and wastes with it. The blood eventually returns to the heart.

The correct functioning of an open circulatory system relies on a very important physical property: The materials carried by the blood, and listed in the previous section, can diffuse effectively over distances of no more than about one millimeter (see Section 6.2 and Dusenbery [8]). Thus an upper limit is set for the size of internal organs; no part of any organ can be more than about 1 mm from the blood. Of course, this also sets a limit on the size of the entire organism; animals with open circulation seldom exceed a few centimeters in size. Typical examples are snails

and houseflies; atypical examples are giant clams and lobsters, but being aquatic, they have the advantage of being bathed in water, which provides for easy waste and CO_2 removal. Further, these large animals have low specific metabolic rates, which minimizes their O_2 and nutrient needs, as well as their production of wastes.

Open circulatory systems are structurally simple, but the size restriction they place on organisms is a major shortcoming. There are plenty of ecological niches into which large animals could fit, especially on land, but to do so has required the evolution of a different kind of circulatory system. We examine that next.

Closed circulatory systems are efficient, but require a powerful heart.

An open circulatory system can be likened to a large fan at the front of a classroom. Air gets moved from the fan toward the rear of the room and it eventually returns to the back of the fan. Most people in the room feel a small breeze from time to time. On the other hand, a *closed circulatory system* can be likened to an enclosed air pump, with a network of conduits that take air directly to each person individually and return the air directly to the pump.

As pointed out above, the problem with open circulation is that most materials can diffuse distances of no more than about one millimeter during biologically realistic times, thus limiting the size of the organism. Closed circulatory systems remove this restriction by taking blood, via tiny vessels, directly to the immediate vicinity of all metabolizing cells. This blood distribution is independent of the size of the organism, how far the cells are from the heart, and how deep the cells are inside an organ.

A vertebrate closed circulatory system contains a heart that pumps blood into a thick-walled artery, called the *aorta*. The latter then progressively branches into smaller arteries and then into capillaries, whose walls are only one cell thick, across which material exchange between blood and other tissues must take place (Figure 9.6.2). Capillaries have such narrow lumens that blood cells must be bent in order to get through. Thus capillaries have the large surface-to-volume ratio necessary for their material exchange function. Eventually, capillaries join together in groups to form small veins that combine into a few large veins and return blood to the heart.

A closed circulatory system is very efficient because it delivers blood right to the doorstep of metabolizing tissues; no cell is very far from a capillary. An important problem is built into closed circulatory systems, however: The frictional resistance to blood flow in the capillaries is much greater that that in arteries. This is true in spite of the fact that the total cross-sectional area of the artery leading from the heart (the aorta) is much less than the total cross-sectional area of all the body's capillaries.

The reason for this apparent contradiction is well known: Blood is viscous and thus adheres to vessel walls as it passes. Only in the center of the vessel lumen is this friction reduced. The difficulty is that capillaries have a very small lumen and a lot of wall area (to increase their material-exchange properties). Therefore, the frictional resistance of capillaries to blood flow is very high. A general rule is that the friction encountered by a viscous material passing through a tube is inversely proportional to the fourth power of the radius of the tube (see (6.2.17) and Vogel [9]). Thus if the

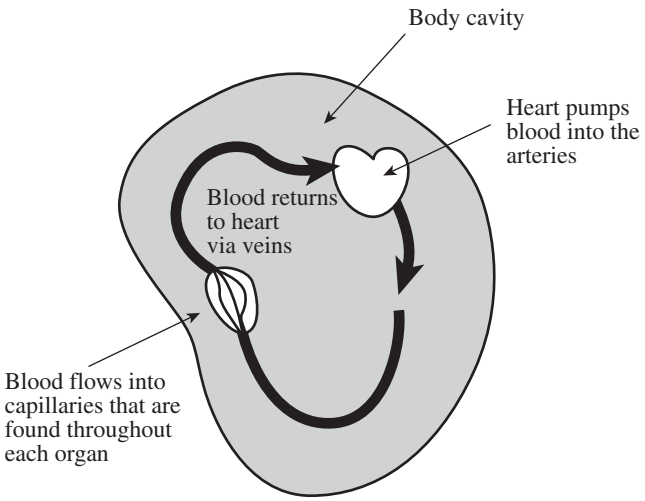


Fig. 9.6.2. A closed circulatory system. The heart pumps blood into a system of arteries, which deliver the blood directly to capillaries in organs. The blood in these capillaries exchanges gases, nutrients, and wastes with tissues in their immediate vicinity. The blood returns to the heart via a system of veins.

radius is halved, the frictional force goes up by 16 times. The end result is that a closed circulatory system requires a very powerful heart to force blood through the many tiny capillaries, in spite of the large total cross-sectional area of the latter.

The cellular fraction of blood serves a variety of functions.

Whole blood has both a liquid fraction, called *plasma*, and a cellular fraction. Plasma is mostly water, but it also contains many inorganic ions, hormones, biochemicals such as sugars, fats, amino acids, and proteins. The levels of all these plasma solutes are critical and thus are maintained at relatively constant levels.

Blood cells are usually classified on the basis of their appearance. All of them originate from common precursor cells in the bone marrow and become specialized later.

(a) *Red blood cells*, or *erythrocytes*, will be of special importance to us in our later discussion of lead poisoning. Mammalian erythrocytes lose their nuclei during formation; the remaining cytoplasm contains large quantities of a biochemical called *hemoglobin*, which has a high affinity for O_2. We introduced the biological role of hemoglobin in Section 6.3; we now elaborate on it.

Erythrocytes pick up O_2 at the lungs:

Reaction 1:[8]

$$\underset{\text{(hemoglobin)}}{\text{Hb}} + O_2 \longrightarrow \underset{\text{(oxyhemoglobin)}}{O_2\text{-Hb}}$$

[8] Recall from Chapter 6 that one hemoglobin molecule can bind up to four O_2 molecules.

The erythrocytes are then carried to the sites of metabolism, where the oxygen is needed, and Reaction 1 is reversed to free the oxygen for use in metabolic processes:

Reaction 2:

$$\mathrm{Hb} + \mathrm{O_2} \longleftarrow \mathrm{O_2\text{-}Hb}$$

Interestingly, the affinity of hemoglobin for CO_2 is fairly low; therefore, most CO_2 is carried from the sites of respiration back to the lungs in the form of carbonic acid or the bicarbonate ion, dissolved in the water of the plasma:

Reaction 3:

$$\mathrm{CO_2} + \mathrm{H_2O} \longrightarrow \underset{\text{(carbonic acid)}}{\mathrm{H_2CO_3}} \longrightarrow \mathrm{H^+} + \underset{\text{(bicarbonate ion)}}{\mathrm{HCO_3^-}}$$

At the lungs, the CO_2 is reconstituted from the bicarbonate ion and carbonic acid, and then exhaled:

Reaction 4:

$$\mathrm{CO_2} + \mathrm{H_2O} \longleftarrow \mathrm{H_2CO_3} \longleftarrow \mathrm{H^+} + \mathrm{HCO_3^-}$$

Reactions 1–4 are related: Reaction 4 takes place at the lungs and raises the blood pH by removing carbonic acid. The rate of Reaction 1 is pH-dependent; conveniently, it goes faster at higher pH. Thus the removal of CO_2 at the lungs promotes the attachment of hemoglobin to O_2. The opposite occurs in metabolizing tissues: The production of CO_2 lowers the blood pH there via Reaction 3, and the lower pH promotes Reaction 2, the release of oxygen from oxyhemoglobin.[9]

While the affinity of hemoglobin for CO_2 is low, its affinity for carbon monoxide (CO) is very high. As a result, the presence of even small amounts of CO can prevent the attachment of O_2 to hemoglobin, accounting for the lethal effect of CO.

The best-studied toxic effect of lead is its role in causing *anemia*, a reduction in erythrocyte concentration. This in turn reduces the oxygen-carrying ability of the blood. The anemia is evidently the result of two processes: First, lead interferes with hemoglobin synthesis, and second, lead causes the lifetimes of mature erythrocytes to be reduced from the usual four months.

(b) *Platelets* are blood cells involved in clotting; they are actually cell fragments that lack nuclei. Platelets collect at the site of an injury and disintegrate. This releases platelet proteins that generate a cascade of reactions, finally resulting in the formation of a clot consisting of a plasma protein called *fibrin*.

(c) *Leukocytes* are nucleated and are often called white blood cells; they are used to fight off infections. One class of leukocytes, the lymphocytes, will be discussed in Chapter 10 in the context of HIV infections. A second group, the granulocytes, functions in certain general responses to infections and allergens.

[9] At least *some* CO_2 does bind to hemoglobin. It has the useful effect that it decreases the oxygen affinity of the hemoglobin (in the vicinity of metabolizing tissues).

There are four overlapping functional paths in our circulation: systemic, pulmonary, lymphatic, and fetal.

Blood cells and plasma can take several routes around the human body, the differences between the routes being both anatomical and functional.

Look at Figure 9.6.3. The mammalian heart has four chambers: The two upper ones are atria and the two lower ones are the muscular *ventricles*. Blood, rich in CO_2 from metabolizing tissues, enters the heart at the right atrium and goes to the right ventricle. The powerful ventricle pushes the blood to capillaries in the lungs; these capillaries surround the many small air sacs (alveoli), which are filled with air when we inhale. Here CO_2 is moved from the plasma into the alveoli for exhalation, and the erythrocytes pick up O_2 from the alveoli; the chemistry for these two processes was outlined in Reactions 1 and 4 in the last section. The blood then returns to the heart at the left atrium. The path of the blood just described—from the heart to the lungs and back to the heart—is called the *pulmonary circulation*.

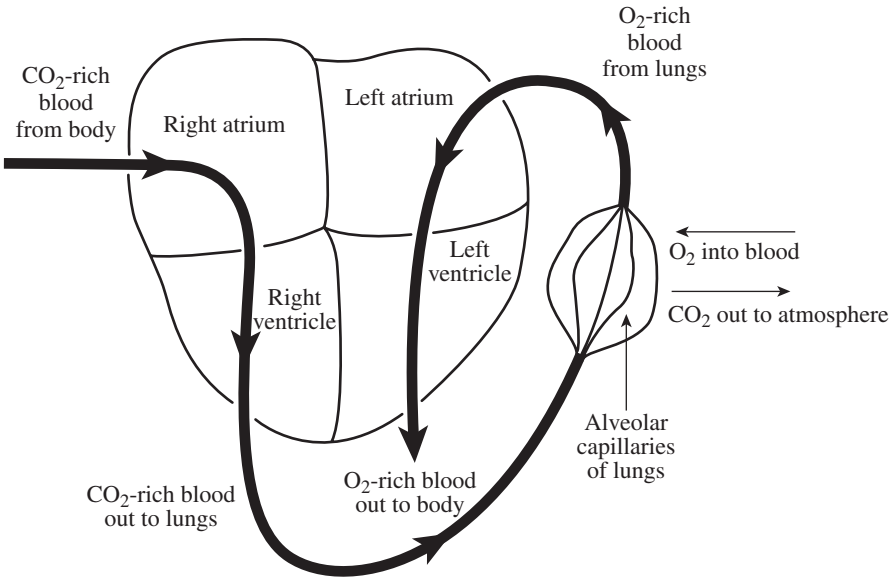


Fig. 9.6.3. The flow of blood through a mammalian heart and lungs. Note that the blood enters and leaves the heart twice.

Pulmonary circulation in outline form:
right ventricle ⟶ pulmonary artery ⟶ lung capillaries ⟶ pulmonary vein ⟶ left atrium

After moving from the left atrium to the left ventricle, blood exits the heart and goes to respiring tissues all over the body via arteries and then capillaries. At the

capillaries, O_2 is given up to the respiring cells and CO_2 is taken from them into the plasma.[10] These reactions were described earlier as Reactions 2 and 3. The blood now returns to the heart by way of veins. The path of blood from the heart to respiring cells and back to the heart is called *systemic circulation*.

Systemic circulation in outline form:
left ventricle ⟶ aorta ⟶ other arteries ⟶ capillaries of respiring tissues ⟶ veins ⟶ right atrium

Note the importance of the powerful ventricles—they must overcome the high frictional resistance that blood meets in the narrow lumens of the capillaries.

Figure 9.6.4 shows a connected group, or *bed*, of capillaries. The lumen of the artery narrows down as the blood approaches the capillaries, and as a result, the frictional resistance increases dramatically. For much of the blood, the effect is almost like hitting a dead end. Consequently, the hydrostatic pressure in the blood at the front (upstream) end of the capillary bed rises sharply. The high hydrostatic pressure pushes some of the liquid fraction of the plasma through gaps in the vessel walls (Figure 9.6.5). The only part of the plasma that cannot be pushed out is the plasma protein fraction, because these molecules are too big. Thus this *interstitial fluid* forced out of capillaries lacks the large plasma proteins.

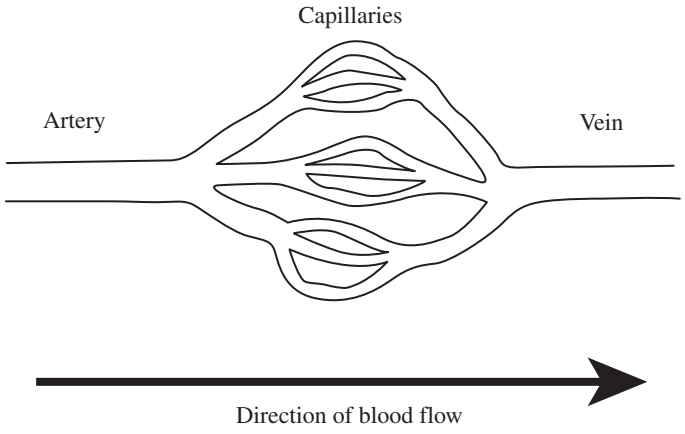


Fig. 9.6.4. A capillary bed. As blood moves from arteries to capillaries, the overall cross-section of the circulatory system increases, but overall frictional resistance increases also.

At the far (downstream) end of the capillary bed, the capillaries join together, friction decreases, and the hydrostatic pressure also decreases. The blood plasma at this point contains everything that the interstitial fluid contains, plus plasma proteins.

[10] The phrase "respiring cells" here means cells that are breaking down sugar to get energy and that are therefore giving off carbon dioxide.

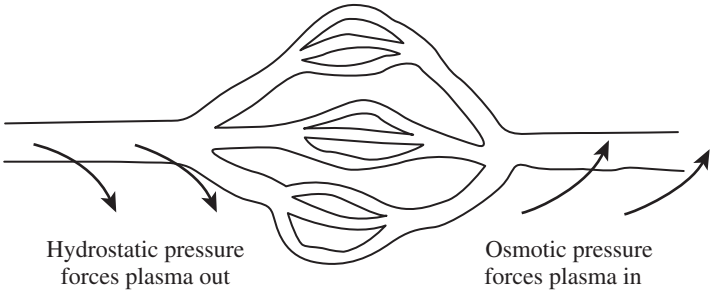


Fig. 9.6.5. The increase in frictional resistance to blood flow imposed by capillaries generates a high hydrostatic pressure upstream from the capillaries. This hydrostatic pressure forces some of the liquid fraction of the blood out of the upstream end of the capillaries and into the surrounding tissues. On the downstream end of the capillaries, the blood, now with a high concentration of dissolved substances, draws some of the liquid from the surrounding tissues back into the circulatory system by osmotic pressure.

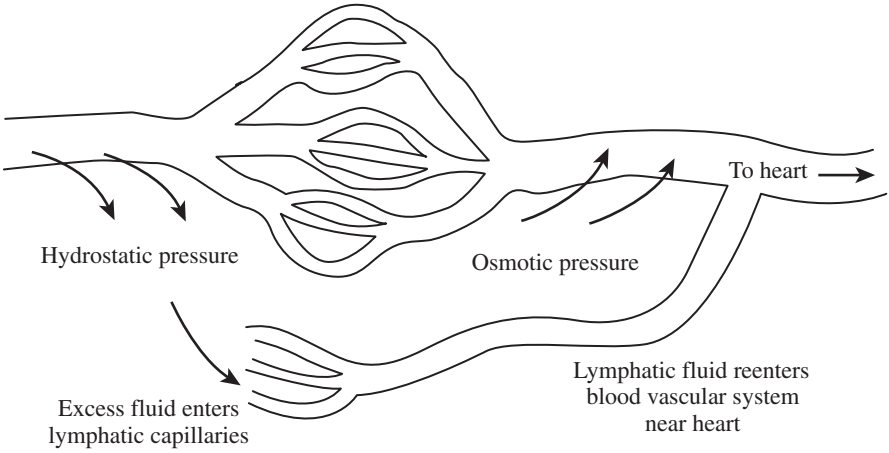


Fig. 9.6.6. Some of the liquid fraction of the blood, forced out of capillaries by hydrostatic pressure, does not return to the blood at the downstream end of the capillaries. This excess is picked up by lymphatic capillaries and eventually returns to the bloodstream near the heart.

Thus the plasma has more dissolved solute than does the interstitial fluid. As a result, most of the interstitial fluid is osmotically drawn back into the vessels to dilute the plasma proteins. Not all the interstitial fluid makes it back to the blood, however; there is a positive pressure differential of several millimeters of mercury between the hydrostatic pressure on the upstream end of the capillary bed and the osmotic pressure on the downstream end. This would cause a buildup of fluid in the tissues if it were not for the fact that there is another path of circulation to collect the excess fluid.

The extra fluid is collected in a set of capillaries of the *lymphatic circulation* and brought by lymphatic veins to the upper body, where they empty into blood veins near the heart (see Figure 9.6.6). During the journey to the heart, the flow of the *lymphatic*

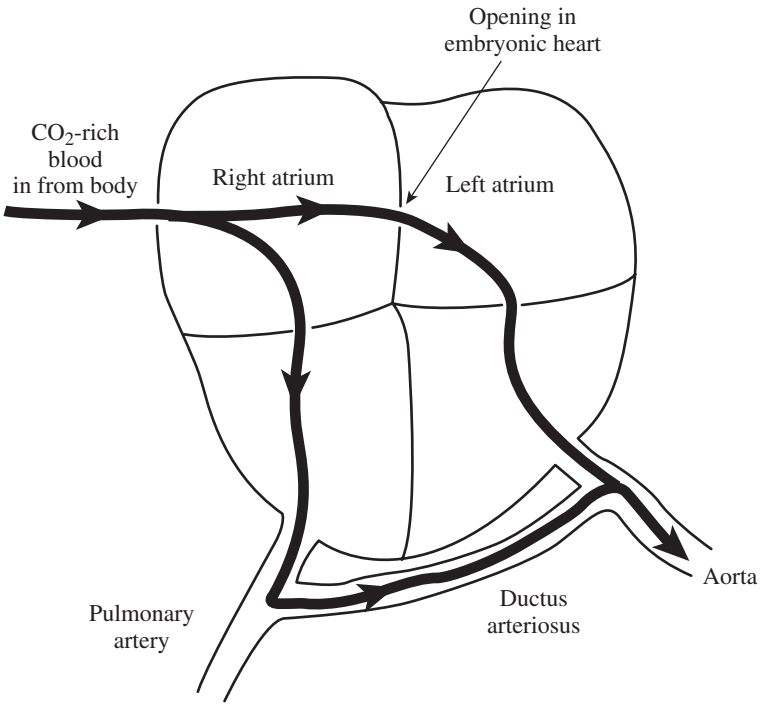


Fig. 9.6.7. A diagram of fetal circulation. An opening between the two atria, and a vessel called the *ductus arteriosus*, shunt fetal blood away from the lungs.

fluid, as the interstitial fluid is called at this point, is pushed by contractions of the nearby skeletal (voluntary) muscles. This movement should be bidirectional, but lymphatic veins have valves that allow flow only toward the heart. Along the way the lymphatic veins pass through *lymph nodes*, packets of lymphatic tissue that filter out pathogens.

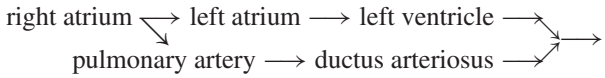
In addition to the interstitial fluid, some white blood cells can also move between the blood circulation and the lymphatic circulation. They do so by squeezing between the endothelial cells that constitute the walls of blood capillaries.

Lymphatic circulation in outline form:
heart $\longrightarrow$ arteries $\longrightarrow$ systemic capillaries $\longrightarrow$ intercellular spaces $\longrightarrow$
lymphatic capillaries $\longrightarrow$ lymphatic veins $\longrightarrow$ blood veins $\longrightarrow$ heart

The fourth path of the circulatory system is found in fetuses and is called the *fetal circulation*. A fetus does not breathe, so its pulmonary circulation is minimized via two shunts: There is an opening in the fetal heart (the foramen ovule), between the right and left atria, that directs blood away from the pulmonary circulation (Figure 9.6.7). Secondly, a special vessel, called the *ductus arteriosus*, carries blood from the pulmonary artery directly to the aorta. Finally, the umbilical artery and vein

carry the fetus's blood to and from the placenta, respectively. All of the above fetal structures close off permanently in the first few minutes after birth.

Fetal circulation in outline form:



aorta ⟶ umbilical artery ⟶ placenta ⟶ umbilical vein ⟶ veins to heart

9.7 Bones

Lead has a strong tendency to localize, or sequester, in bones; its half-life there is about 20 *years. Thus the skeleton can serve as a chronic systemic source of lead long after the original exogenous lead exposure.*

Bones are not static. Besides producing blood cells, they are being "remodeled" in response to our physical activities throughout our lives. In this section, we will examine the anatomy, function, and growth of bones.

Bones support, protect, and move.

The set of our bones is called our *skeleton*. It supports the rest of our body structure. All large terrestrial animals require an internal skeleton because the nonskeletal tissue would collapse under its own weight and a hard external skeleton (like an insect's) would weigh too much. Our skeleton surrounds our internal organs, protecting them from mechanical injury. In the cases in which organs are not protected by bone, e.g., eyeballs and testicles, reflexive reactions and very low pain thresholds are necessary for protection. With the aid of our voluntary muscles, we can use our skeleton to project effects at a distance—walking, reaching, and hugging, for instance.

Bone marrow is the source of blood cells.

In the earlier section on the circulatory system a number of blood cells were described. All of these cells originate from a single variety of cell in the core, or *marrow*, of bones. These cells are called *stem cells*, and they divide rapidly, generating large numbers of daughter cells. The subsequent fate of a daughter cell depends on the conditions of its maturation environment. Some lymphocytes, for instance, mature in the thymus gland, just behind the breastbone of children. Red blood cells mature in the marrow, synthesize hemoglobin, and then (in mammals) lose their nuclei. We will have more to say about blood cell origins in Chapter 10.

Bony tissue is replaced throughout life.

There are special cells, called *osteoblasts*, in bone that secrete a protein about which the compound *hydroxyapatite* (mainly calcium phosphate) crystallizes; thus hard

bone is formed. When the muscles to which a bone is attached become stronger, the stresses cause the bone to thicken to adapt to the new need. This is initiated by another group of cells, called *osteoclasts*, which secrete chemicals to dissolve hard bone tissue. Osteoblasts then reconstitute the bone in a new, thicker form.[11] It has been estimated that our bones are replaced up to ten times in our lives.

Virtually all bone growth after adolescence affects the thickness of a bone. Bone growth before that time may be in thickness, but may also be in the length of the bone, accounting for the dramatic rate of change in a child's height.

Lead tends to be deposited in the region of bones near their ends, as revealed by X-ray pictures. The lead is then very slowly released over a period of many years. This long half-life means that lead tends to accumulate in bones. Indeed, about 95% of a person's total-body lead can be found in the bones [2].

9.8 The Kidneys

Our kidneys provide a mechanism for ridding the body of water-soluble substances. They are very selective, however: They can maintain a constant chemical composition in our bodies by removing materials in excess and retaining materials in short supply. Thus we should correctly expect that the kidneys would help to excrete lead. The problem is that much lead becomes sequestered in bone and is therefore not solubilized in blood where the kidneys can get at it. Nevertheless, if absorbed lead is to be removed from the body, kidney excretion will be the major route out.

The kidneys remove nitrogenous wastes and help regulate the concentration of materials in the blood.

When we eat protein, e.g., the muscle from a cow's leg, the process of digestion breaks the protein down into its component compounds, called *amino acids*. In our bodies, amino acids have two possible fates: First, they can be incorporated into our own proteins. We can synthesize most, but not all, of the amino acids we need from related precursors we get in our diet. Second, ingested amino acids can be broken down to extract some of their energy. In this section, we will be concerned with one aspect of the latter of these two fates—the removal of a certain chemical group ($-NH_2$) from an amino acid prior to extraction of the amino acid's energy.

Unless it is to be used in the synthesis of other nitrogenous compounds in our bodies, the amino group ($-NH_2$) of ingested amino acids must be removed from our body as waste. The problem is that the amino group quickly forms *ammonia* (NH_3), which is toxic. Aquatic animals can get rid of ammonia by releasing it directly into the surrounding water, in which the ammonia is highly soluble. Many terrestrial animals, humans included, convert the ammonia to urea (H_2NCOH_2), which is moderately

[11] It should now be evident how archaeologists can tell so much about an animal by examining a few bones. The pattern of bumps and thickenings on a bone constitute a graphic history of the animal's life.

water-soluble and much less toxic than ammonia.[12] The urea is then removed from our bodies by our kidneys in urine.

At the kidneys, blood pressure forces some of the liquid fraction of blood into small kidney tubules (see Figure 9.8.1). This liquid contains water, ions, many essential biological molecules, and, of course, urea. As the liquid moves along these convoluted tubes, most of the water and most of the desirable dissolved substances are resorbed back into the blood. The aqueous liquid left behind in the kidneys is *urine*, which contains a high concentration of urea. Urine also contains other dissolved substances that the blood has in excess of normal needs. Thus the kidneys serve the *homeostatic function* of maintaining the concentration of dissolved substances in the blood and other tissues at normal levels.[13]

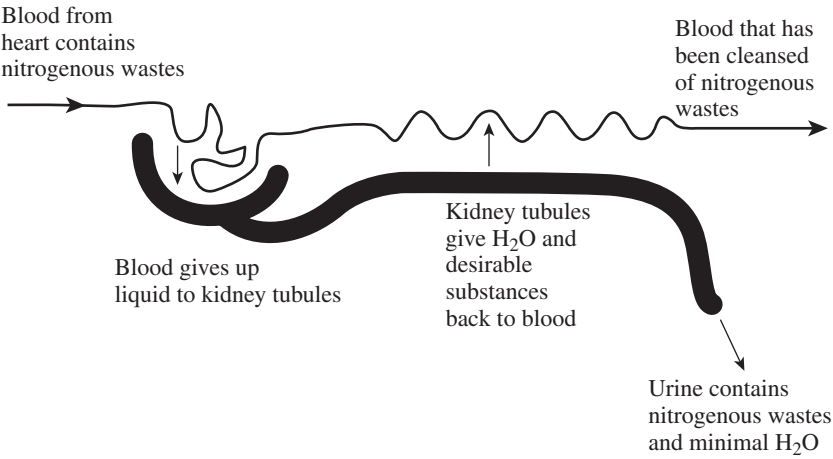


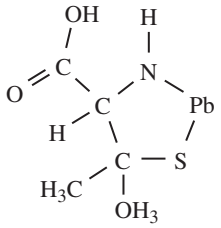
Fig. 9.8.1. A simplified model of the mammalian kidney. Blood pressure at the kidneys forces some of the liquid fraction of the blood into kidney tubules. This liquid fraction contains wastes, but also contains useful solutes, such as sugars. Later, the kidney takes back the useful substances and most of the water, leaving urine with the concentrated wastes (to be voided).

Lead is absorbed into bones about 100 times faster than it is released. Thus an important therapeutic approach to lead poisoning is to try to prevent the lead from becoming sequestered in bone, from which it would be slowly released back into the blood over a period of decades. The trick is to make the lead very soluble shortly after exposure so the kidneys can excrete it efficiently. There is a class of chemical compounds, called *metal chelates*, that react rapidly with lead and many

[12] Egg-laying animals go one step further and convert the urea to uric acid, which is water-insoluble. Thus uric acid can accumulate inside an avian or reptilian egg and not harm the fetus prior to hatching.

[13] Patients with *diabetes mellitus* produce insufficient quantities of the protein *insulin*. This leads to an excess of the sugar glucose in their blood. The kidneys remove some of the excess *glucose* in urine—thus providing a means of medical diagnosis.

other metals to form very soluble compounds that the kidneys can excrete. *Penicillamine*, for example, can be administered orally, and the compound it forms with lead, penicillamine-lead, is highly soluble in water. The structure of penicillamine-lead is shown here:[14]



In summary, kidneys first remove most dissolved materials, both useful and waste, from the blood and later put the useful materials back into the blood. We could easily imagine a simpler system, in which only a small amount of water, all the urea, and any other material in excess is removed directly, without benefit of resorption, but that is not how our kidneys work. The forces of evolution do not necessarily yield the simplest system, but instead yield a modification of a preexisting system. This frequently generates a more complicated system, but if the new system provides a selective advantage, it can become fixed in the population.

Lead has been shown to have a direct pathological effect on kidney function. Acute exposure in children leads to malfunctioning of the resorption process, resulting in a high concentration of glucose and other desirable compounds in the urine. Chronic lead exposure eventually results in general kidney failure.

9.9 Clinical Effects of Lead

Lead poisoning is indicated by a variety of clinical symptoms, including gastrointestinal and mental disorders.

Lead poisoning causes a wide variety of general symptoms.

We conclude with a short description of symptoms of lead poisoning that a physician might see in a patient. In adults, there are gastrointestinal disorders such as vomiting and pain. In children, there are central nervous system disorders, e.g., drowsiness, irritability, and speech disturbances, as well as gastrointestinal symptoms. An interesting symptom in some cases is a blue line along the gums, formed when lead reacts with sulfur, the accumulation of the latter being associated with poor dental hygiene.

The effect of lead on IQ is an interesting one. As mentioned above, lead-induced neurophysiological disorders are especially noted in children. This is not unexpected because lead seems to affect the velocity of nerve impulse conduction. Evidence suggests that lead poisoning can reduce a child's IQ by about five points.

[14] Chelating agents are not without risks: A chelating agent that picks up lead may also pick up other divalent metals, e.g., calcium. Loss of blood calcium can lead to uncontrollable muscle tremors and even death.

9.10 A Mathematical Model for Lead in Mammals

While lead interacts differently with the various tissues of the body, as a first approximation we need only distinguish three tissue types: bone, blood, and the other soft tissue of the body. Bone tends to take up lead slowly but retain it for very long periods of time, in contrast to soft tissue, other than blood, in which the turnover of lead is much quicker. Blood is the transport agent of the metal. The disposition of lead in the body can be followed as a three-compartment system by tracking its movement into and out of these three tissue types. In this section we analyze such a model proposed by Rabinowitz, Wetherill, and Kopple.

The uptake and movement of lead can be modeled by the use of compartments.

The activity of lead in the body depends on the tissue in which it is located (recall the end of Section 9.1). To construct a mathematical model for the movement of lead, at least three distinct tissue types must be recognized: bone, blood, and soft tissue (other than blood).[15] These will be our mathematical compartments. Lead enters the system by ingestion and through the skin and lungs. These intake paths usher the substance to the blood. From the blood, lead is taken up by bone and by soft tissue. This uptake is reversible: Lead is also released by these organic reservoirs back to the blood. However, especially for bone, lead's half-life in that tissue is very long. Lead can be shed from the body via the kidneys from the blood and to a lesser extent, through hair. Thus blood is the main conduit through which lead moves among our compartments.

To begin the model, let compartment 1 be the totality of the victim's blood, compartment 2 the soft tissue, and compartment 3 the skeletal system. We must also treat the environment as another compartment to account for lead intake and elimination; we designate it as compartment 0. Let x_i, $i = 1, \ldots, 3$, denote the amount of lead in compartment i and let a_{ij}, $i = 0, \ldots, 3$, $j = 1, \ldots, 3$, denote the rate of movement of lead *to* compartment i *from* compartment j. The product $a_{ij}x_j$ is the rate at which the amount of lead increases in compartment i due to lead in compartment j. There is no reason that a_{ij} should equal a_{ji}, and as noted above, the rate of movement from blood to bone is very different from the reverse rate. The units of the a_{ij}s are per day.

Because we will not keep track of the amount of lead in the environment, this is an *open compartment* model. Instead, we account for environmental intake by including a separate term, $I_L(t)$, applied to compartment 1, the blood. From the discussion above, some of the rates are zero; namely, $a_{03} = a_{23} = a_{32} = 0$, signifying no direct elimination to the environment from bone and no direct exchange between bone and soft tissue. In addition, all rates a_{i0} are 0, since there is no x_0 term. Finally, there is no need for terms of the form a_{ii}, since a compartment is our finest unit of resolution.

With these preparations, we may now present the model that derives from the simple fact that the rate of change of lead in a compartment is equal to the difference

[15] As in the discussion ending Section 9.1, throughout this section, by soft tissue, we mean soft tissue other than blood.

between the rate of lead entering and the rate leaving:

$$\begin{aligned}\frac{dx_1}{dt} &= -(a_{01}+a_{21}+a_{31})x_1 + a_{12}x_2 + a_{13}x_3 + I_L(t),\\ \frac{dx_2}{dt} &= a_{21}x_1 - (a_{02}+a_{12})x_2,\\ \frac{dx_3}{dt} &= a_{31}x_1 - a_{13}x_3.\end{aligned} \tag{9.10.1}$$

In words, the first equation, for example, says that lead leaves the blood for the environment, soft tissue, and bone at a rate in proportion to the amount in the blood; lead enters the blood from the soft tissue and bone in proportion to their respective amounts; and lead enters the blood from the environment according to $I_L(t)$. The algebraic sum of these effects is the rate of change of lead in the blood. In line with our discussion of Section 2.4, this system can be written in matrix form as

$$\mathbf{X}' = A\mathbf{X} + \mathbf{f}. \tag{9.10.2}$$

Here $\mathbf{X}$ is the vector of xs, $\mathbf{f}$ is the vector

$$\mathbf{f} = \begin{bmatrix} I_L(t) \\ 0 \\ 0 \end{bmatrix},$$

and A is the 3×3 matrix

$$A = \begin{bmatrix} -(a_{01}+a_{21}+a_{31}) & a_{12} & a_{13} \\ a_{21} & -(a_{02}+a_{12}) & 0 \\ a_{31} & 0 & -a_{13} \end{bmatrix}.$$

From (2.4.12), the solution is

$$\mathbf{X} = e^{At}\mathbf{X}_0 + e^{At}\int_0^t e^{-As}\mathbf{f}(s)ds. \tag{9.10.3}$$

We will now suppose that the intake of lead, $I_L(t)$, is constant; this is a reasonable assumption if the environmental load remains constant. Then $\mathbf{f}$ is also constant, and we may carry out the integration on the right-hand side of (9.10.3). In keeping with the result that $-a^{-1}e^{-at}$ is the integral of the ordinary exponential function e^{-at}, we get

$$\begin{aligned} e^{At}\int_0^t e^{-As}\mathbf{f}(s)ds &= e^{At}[-A^{-1}e^{-As}]\Big|_0^t \mathbf{f} \\ &= -e^{At}[e^{-At} - I]A^{-1}\mathbf{f} \\ &= -[I - e^{At}]A^{-1}\mathbf{f}. \end{aligned}$$

Substitution of this result into (9.10.3) gives

$$\mathbf{X} = e^{At}\mathbf{X}_0 - [I - e^{At}]A^{-1}\mathbf{f} = e^{At}[\mathbf{X}_0 + A^{-1}\mathbf{f}] - A^{-1}\mathbf{f}. \tag{9.10.4}$$

This is the solution of system (9.10.1), provided A^{-1} exists. We can obtain solutions provided that the exponential e^{At} is computable.[16]

The long-term predictions of the model.

Recall from the discussion of Section 2.6 that the long-term behavior of the solution is predicted by knowledge of the eigenvalues of the matrix A. But it is easily seen that this is a compartment matrix (cf. Section 2.6). The diagonal terms are all negative, the first column sum is $-a_{01}$, the second column sum is $-a_{02}$, and the third column sum is 0. Therefore, by the Gershgorin circle theorem, the eigenvalues of A have negative or zero real parts. In the case that they are all strictly negative, then the exponential e^{At} tends to the zero matrix as $t \to \infty$. As a result, the long-term fate of the lead in the body is given by the term $A^{-1}\mathbf{f}$,

$$\mathbf{X} \to -A^{-1}\mathbf{f} \quad \text{as } t \to \infty. \tag{9.10.5}$$

A study on human subjects.

Rabinowitz, Wetherill, and Kopple studied the lead intake and excretion of a healthy volunteer living in an area of heavy smog. Their work is reported in [3] and extended by Batschelet, Brand, and Steiner in [11]. (See also [12].) The data from this study were used to estimate the rate constants for the compartment model (9.10.1). Lead is measured in micrograms and time in days. For example, the rate 49.3 is given below as the ingestion rate of lead in micrograms per day, and the other coefficients are as given in Table 9.10.1.

Table 9.10.1. Lead exchange rates.

coefficients	a_{01}	a_{12}	a_{13}	a_{21}	a_{02}	a_{31}	I_L
value	0.0211	0.0124	0.000035	0.0111	0.0162	0.0039	49.3

This model has significant biological implications. The output of the computation of the exponential of this matrix does not seem to merit printing. More important for the purposes of understanding this model is the graph of the solutions. These graphs are shown in Figure 9.10.1. This figure shows graphs of the total lead in compartments 1, 2, and 3 over a period of 365 days. The horizontal axis is days and the vertical axis is in units of micrograms of lead.

Our calculation of the solution for (9.10.1) follows the procedure of (9.10.4) exactly. As we will see, the eigenvalues for this matrix are negative. Further, since the trend of the solution is independent of the starting condition—recall (9.10.5)—we take the initial value to be

[16] See [10] for a delightful discussion of the problems involved.

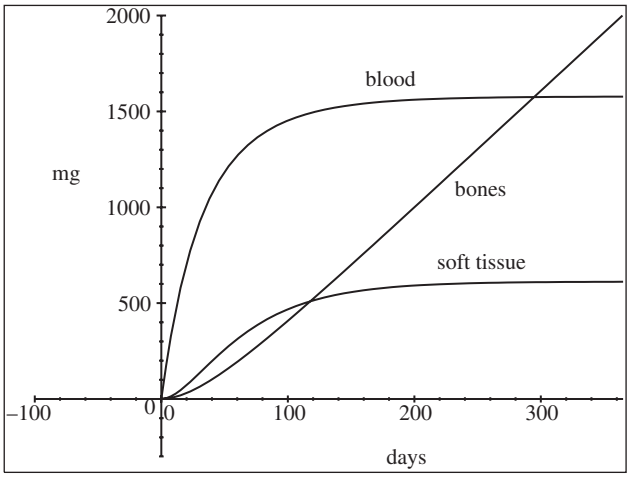


Fig. 9.10.1. Solutions for (9.10.1).

$$X_0 = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}.$$

The solution is computed and graphed with

```
  MAPLE
> with(LinearAlgebra):
> A:=Matrix(3,3,[-0.0361, 0.0124, 0.000035, 0.0111, -0.0286, 0.0, 0.0039, 0.0, -0.000035]);
> etA:=MatrixExponential(A,t);
> AinvF:=evalm(MatrixInverse(A)&*vector([493/10,0,0]));
> u:=evalm(-AinvF+etA&*AinvF);
> plot({u[1](t),u[2](t),u[3](t)},t=0..365);

  MATLAB
> A=[-0.0361 0.0124 0.000035; 0.0111 -0.0286 0.0; 0.0039 0 -0.000035];
> f=[49.3; 0; 0]; % column vector
> t=0:2:366; % in steps of 2
  % make an m-file, At.m, with function Y=At(A,t), Y=t*A;
> AinvF=inv(A)*f;
  % make up the sequence of solution vectors
> u=[]; s=size(t);
> for i=1:s(2)
    u=[u,-AinvF+expm(At(A,t(i)))*AinvF];
  end
> plot(t,u)
```

One observation is that the level of lead in the blood and soft tissue approaches the steady state quickly. Lead achieves a steady state in the blood of about 1800 units and about 700 in the soft tissue. The level of lead in the bones continues to rise after a period of one year. In this model, the bones continue to absorb lead because of the constant rate of input. On the other hand, the bones release lead slowly and steadily. As we have already seen in the discussion in Section 9.9, a high level of lead in the bones has implications for severe and chronic biological problems.

The levels of lead in the steady state is the next subject for discussion. For this lead model, the long-term behavior of solutions can be computed as follows:

MAPLE
```
> lambda:=Eigenvals(A):
```

MATLAB
```
> [evect,eval]=eig(A)
```

This computation yields

$$-0.0447, \qquad -0.02, \quad \text{and} \quad -0.00003.$$

We find that the eigenvalues for the matrix A associated with the lead problem are all negative. Further, a computation of $-A^{-1}\mathbf{f}$

MAPLE
```
> leadlim:=evalm(-AinvF);
```

MATLAB
```
> leadlim=-AinvF
```

yields

$$-A^{-1}\mathbf{f} = (1800, 698, 200582), \quad \text{where } \mathbf{f} = \left(\frac{439}{10}, 0, 0\right).$$

Hence this model predicts the long-range forecast summarized as follows: The levels of lead in the blood will rise to about 1800 micrograms, the level of lead in the other soft tissues will rise to about 698 micrograms, and the level of lead in the bones will rise to about 200582 micrograms.

It should be recognized that the coefficients for our absorption of lead are not constants. By way of data for long-range forecast, Ewers and Schlipkoter point out that after age 20, the lead content of most soft tissue does not show age-related changes [1]. The lead content of bones and teeth increases throughout life, since lead becomes localized and accumulates in human calcified tissues (bone and teeth). This accumulation begins with fetal development and continues to approximately the age of 60 years. At least for adults, various studies show that approximately 95% of the total body lead is lodged in the bones.

Exercises/Experiments

1. This exercise is an investigation of the lead model. The exercise is broken into a set of questions that can be answered by modification of the syntax in this chapter.
   (a) What is the long-range forecast for lead in each of the compartments using model (9.10.1)?
   (b) Approximately what is the lead level achieved in each of the compartments in "1 year"?
   (c) Ewers and Schlipkoter state that 95% of the total body lead of human adults is lodged in bones [1]. Schroeder and Tipton state that "Bones contain 91% of the total body lead" [4]. What percentage of the total body lead does this model place in the bones?
   (d) Redo (a) and (b) by doubling or halving the ingestion rate. What is the revised long-range forecast for each of the compartments? Approximately what is the revised lead level achieved in each of the compartments in "1 year"?

2. All the remaining questions are concerned with a person that has lived in a lead-contaminated environment so long that a level of 2500 micrograms of lead has accumulated in the bones. You may continue to assume that in the contaminated environment 49.3 micrograms per day are absorbed. In their 1968 paper, Schroeder and Tipton stated that an average of 17 micrograms of lead are retained per day. We take this absorption rate to be that in a "clean'' environment.

(a) What level of lead do you expect in the tissue and bones for a person living in a contaminated environment long enough that 2500 micrograms of lead has accumulated in the bones?

(b) Suppose that this person described in the previous question is moved to a relatively lead-free environment. What is the approximate level of lead in the bones, tissue, and blood at the end of one year after living in this new environment?

(c) We have seen that there are drugs that alleviate the effects of lead in the bones by increasing the rate of removal from the bones. What should that rate be to cut in half the amount of lead in the bones at the end of one year in the cleaner environment?

(d) Suppose that the person takes the drug you have designed but is not moved to the cleaner environment. What are the levels of lead in the bones, tissue, and blood after one year of taking the drug while living in the contaminated environment?

(e) Ewers and Shlipkoter give the half-life of lead in blood as 19 days, in soft tissue as 21 days, and in bones as 10 to 20 years [1]. What is the half-life as assumed in our model?

(f) According to this model, what percentage of the lead ingested into the body is returned to the environment during the 100th day in the initial situation?

9.11 Pharmacokinetics

The routes for dispersion of drugs through the body follow the same pattern as those of lead. The previous section followed lead through the body. The model of this section examines how the body handles the ingestion of a decongestant. We keep track of this drug in two compartments of the body: the gastrointestinal tract and the circulatory system. The mathematical importance of this model is that the limit for the system is a periodic function.

A two-compartment pharmacokinetic model is used to construct a drug utilization scenario.

Among all the means for the delivery of therapeutic drugs to the bloodstream, oral ingestion/gastrointestinal absorption is by far the most popular. In this section, we study this delivery mechanism, following closely the work of Spitznagel [13]. The working hypothesis of the study is the following series of events. The drug is taken

orally on a periodic basis resulting in a *pulse* of dosage delivered to the gastrointestinal (GI) tract. From there, the drug moves into the bloodstream, without delay, at a rate proportional to its concentration in the GI tract and independent of its concentration in the blood. Finally, the drug is metabolized and cleared from the blood at a rate proportional to its concentration there.

Evidently, the model should have two compartments: Let $x(t)$ denote the concentration of drug in the GI tract and $y(t)$ its concentration in the blood. In addition, we need the drug intake regimen; denote by $D(t)$ the drug dosage, as seen by the GI tract, as a function of time t.[17] The governing equations are

$$\begin{aligned} \frac{dx}{dt} &= -ax + D, \\ \frac{dy}{dt} &= ax - by. \end{aligned} \tag{9.11.1}$$

Since the equations in (9.11.1) constitute a linear system with forcing function $D(t)$, its solution, in matrix form, is given by (2.4.12), which we repeat here:

$$\mathbf{Y} = e^{Mt}\mathbf{Y}_0 + e^{Mt}\int_0^t e^{-Ms}\mathbf{P}(s)ds. \tag{9.11.2}$$

In this equation, $\mathbf{Y}$ and $\mathbf{P}$ are the vectors

$$\mathbf{Y} = \begin{bmatrix} x \\ y \end{bmatrix} \quad \text{and} \quad \mathbf{P} = \begin{bmatrix} D(s) \\ 0 \end{bmatrix},$$

and M is the coefficient matrix

$$\begin{bmatrix} -a & 0 \\ a & -b \end{bmatrix}.$$

Note that as a compartment model, the diagonal terms of this matrix are negative and the column sums are negative or zero. Consequently, the first term of the solution, $e^{Mt}\mathbf{Y}_0$, is transient, that is, it tends to 0 with time. Therefore, asymptotically the solution tends to the second term,

$$\mathbf{Y} \to e^{Mt}\int_0^t e^{-Ms}\begin{bmatrix} D(s) \\ 0 \end{bmatrix} ds, \tag{9.11.3}$$

which is periodically driven by D.

Periodic solutions predict serum concentration cycles.

In conjunction with specific absorption and metabolism rates for a given drug, system (9.11.1) and its solution, (9.11.2), may be used to predict cycles of drug concentration in the blood. Fortunately, the required data are available for a variety of drugs, such as PPA and CPM, as reported and defined in [13]. As mentioned above, the exact

[17] With the use of time-release capsules, a drug may not be immediately available to the GI tract even though the medication has been ingested.

shape of the dosage profile, $D(t)$, depends on how the producer, the pharmaceutical company, has buffered the product. We assume that the drug is taken every six hours (four times a day) and dissolves within about $\frac{1}{2}$ hour, providing a unit-pulse dosage with height 2 and pulse width $\frac{1}{2}$ on the interval $[0, 6]$; see Figure 9.11.1. The rate parameters a and b are typically given as half-lives; cf. (3.5.8). For PPA, we use a $\frac{1}{2}$-hour half-life in the GI tract, so $a = 2\ln(2)$, and a 5-hour half-life in the blood, $b = \frac{\ln(2)}{5}$.

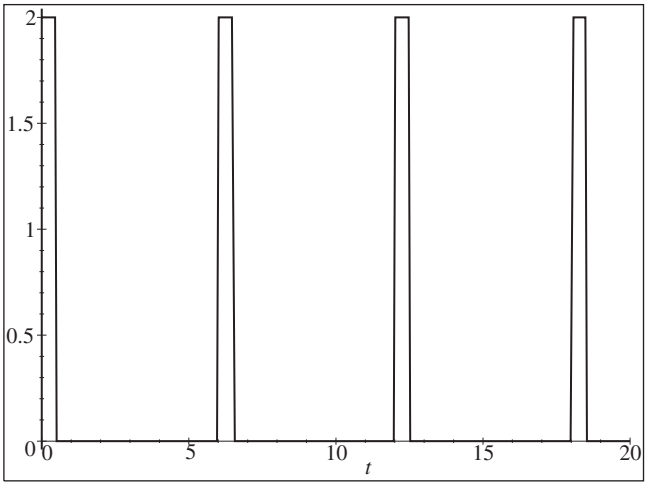


Fig. 9.11.1. Graph of drug dosage $D(t)$.

For a numerical solution, we take zero initial conditions, $x(0) = y(0) = 0$, that is, initially no drug is present in the GI tract or circulatory system, and use a Runge–Kutta method to obtain Figure 9.11.2. The behavior of $x(t)$ is the lower graph and predicts an oscillating increase and decrease of concentration in the GI tract. On the other hand, the concentration in the circulatory system, $y(t)$, is predicted to be an oscillation superimposed on a gradually increasing level of concentration.

MAPLE

```
> restart;
> a:=ln(2)*2; b:=ln(2)/5;
> Dose1:=t->sum((signum(t-n*6)-signum(t-(n*6+1/2))),n=0..10);
> plot(Dose1(t),t=0..20);
> with(plots): with(DEtools):
> J:=DEplot({diff(x(t),t)=Dose1(t)-a*x(t),diff(y(t),t)=a*x(t)-b*y(t)},{x(t),y(t)},t=0..50,{[0,0,0]},stepsize=0.5,
            scene=[t,x],linecolor=RED):
> K:=DEplot({diff(x(t),t)=Dose1(t)-a*x(t),diff(y(t),t)=a*x(t)-b*y(t)},{x(t),y(t)},t=0..50,{[0,0,0]},stepsize=0.5,
            scene=[t,y],linecolor=BLACK):
> plots[display]({J,K});
```

MATLAB

```
% make up an m-file dose.m with
% function H=dose(t)
% H=0;
% for n=0:50
```

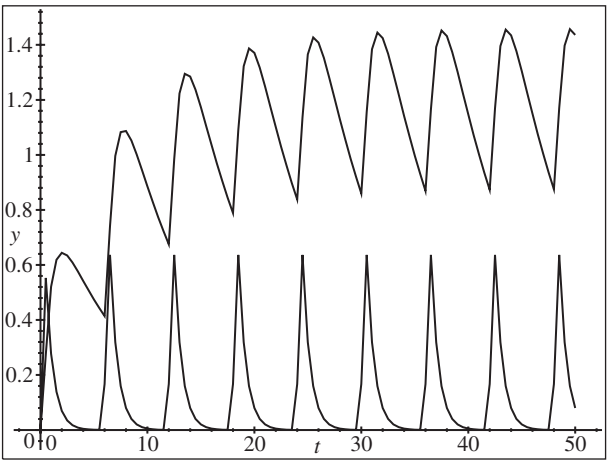


Fig. 9.11.2. Loading of the bloodstream and the GI tract from a dosage regime.

```
  %   if (t >= 6*n)&(t < 6*n+.5)
  %      H=1;
  %   end
  % end
> t=0:.05:50; s=size(t);
> for k=1:s(2)
     Dvect(k)=2*dose(t(k));
  end
> plot(t,Dvect) % Figure 9.11.1
  % make up an m-file drugRate.m as
  % function Yprime=drugRate(t,x); a=2*log(2); b=log(2)/5;
  % Yprime=[-a*x(1)+2*dose(t); a*x(1)-b*x(2)];
> [t,Y] = ode23('drugRate',[0 50],[0;0]);
> plot(t,Y) % Figure 9.11.2
```

In Figure 9.11.3, we show the phase-plane plot, x vs. y, of this solution. It shows that, asymptotically, the solution tends to a periodic (but nonsinusoidal) oscillation; this is called a *limit cycle*.

```
  MAPLE
> phaseportrait([diff(x(t),t)=Dose1(t)-a*x(t), diff(y(t),t)=a*x(t)-b*y(t)],[x(t),y(t)],t=0..50,{[0,0,0]},stepsize=0.5);

  MATLAB
> plot(Y(:,1),Y(:,2))
```

From the figure, the high concentration level in the blood is about 1.8, while the low is about 1.1 on the limit cycle. In designing a drug, it is desirable to keep the concentration as uniform as possible and to come up to the limit cycle as quickly as possible. Toward that end, the parameter a can be more easily adjusted, for example by a "time release" mechanism. The parameter b tends to be characteristic of the drug itself.

The asymptotic periodic solution may be found from (9.11.3) or by the following manual scheme.

We can solve for $x(t)$ explicitly. There are two parts: one part for $0 < t < \frac{1}{2}$, where the dosage function has value 2, and the other part for $\frac{1}{2} < t < 6$, where the

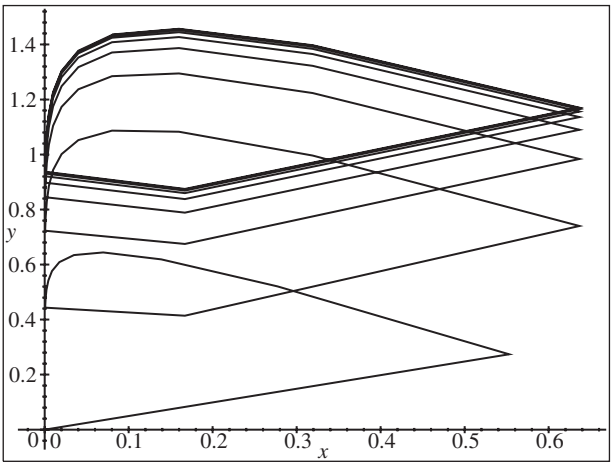


Fig. 9.11.3. $\{x(t), y(t)\}$ with limit cycle.

dosage function has value 0. We call the first part $x_1(t)$ and find the solution here. In this case, the input from $D(t)$ is 2 and the initial value for the periodic solution is yet unknown. Call the initial value x_0. We have

$$x(t) = -ax(t) + 2$$

with $x(0) = x_0$.

```
MAPLE (symbolic)
> dsolve({diff(x(t),t)+a*x(t)=2,x(0)=x0},x(t));
> x1:=unapply(op(2,%),t);
> simplify(x1(t));
```

Noting that $2^{2t} = 4^{-t}$, we see that this equation has solution

$$x_1(t) = \frac{1}{\ln(2)} + \left(x_0 - \frac{1}{\ln(2)}\right) 2^{-2t}.$$

Follow this part of the solution from $t = 0$ to $t = \frac{1}{2}$. Next, we compute the solution $x(t)$ for (9.11.1) with $\frac{1}{2} < t < 6$. In this case, the input from $D(t) = 0$ and the initial value for the continuation of the periodic solution starts where the first part left off. Thus

$$x(t) = -ax(t)$$

with

$$x\left(\frac{1}{2}\right) = x_1\left(\frac{1}{2}\right).$$

```
MAPLE (symbolic)
> dsolve({diff(x(t),t)+a*x(t)=0,x(1/2) = x1(1/2)},x(t));
> x2:=unapply(op(2,%),t);
> simplify(x2(t));
```

This differential equation has solution

$$x_2(t) = 2^{-2t}\left(x_0 + \frac{1}{\ln(2)}\right).$$

In order for $x(t)$ to be a periodic solution for (9.11.1) with period 6, it should be true that $x_0 = x(0) = x(6)$. We find x_0 by setting $x_1(0) - x_2(6)$ equal to zero and solving for x_0:

```
  MAPLE
> x0:=solve(x2(6)-x0=0,x0);

  MATLAB
  % In MATLAB we must use a numerical technique; bisection is straightforward
  % start with a value too low, xleft, and one too high xright, try the midpoint xmid, adjust from there
  % make an m-file drugXRate.m as follows:
  %   function xprime=drugXrate(t,x)
  %   a=2*log(2); xprime=-a*x(1)+2*dose(t);
> xleft=0; xright=1;
> for k=1:16
>    xmid=(xleft+xright)/2;
  % solve ode on 0 to 0.5
>    [t,x]=ode23('drugXrate',[0 .5],xmid); s=size(x); x05=x(s(1)); % save the ending value of x
  % solve ode on 0.5 to 6 with that ending value as starting value
>    [t,x]=ode23('drugXrate',[.5 6],x05); s=size(x); x6=x(s(1)); % save the final ending value
  % we want x6 to equal xmid; adjust if too big or too small
>    if x6 > xmid % end value bigger than start
>       xleft=xmid; % raise the start value
>    else
>       xright=xmid; % lower the start value
>    end
> end
> x0periodic=xmid
```

The solution is

$$x_0 = \frac{1}{\ln(2)\cdot 4095}.$$

It remains to find the periodic solution y for the second equation. Equation (9.11.2) can be rewritten, now that we have a formula for $x(t)$:

$$y(t) + by(t) = ax(t).$$

The function $y_1(t)$ will be the solution for $0 < t < \frac{1}{2}$ and $y_2(t)$ is the solution for $\frac{1}{2} < t < 6$.

Now continue the solution for $\frac{1}{2} < t < 6$ and for $y(\frac{1}{2}) = y_1(\frac{1}{2})$:

```
  MAPLE
> dsolve({diff(y(t),t)=a*x1(t)-b*y(t), y(0) = y0},y(t));
> simplify(rhs(%)); y1:=unapply(%,t);
> dsolve({diff(y(t),t)=a*x2(t)-b*y(t), y(1/2)=y1(1/2)},y(t));
> y2:=unapply(op(2,%),t);
  # require that y2(6)=y1(0)
> solve(y2(6)=y0,y0); y0:=evalf(%);

  MATLAB
  % now find y0periodic
> yleft=0; yright=1;
> for k=1:16
>    ymid=(yleft+yright)/2; [t,Y]=ode23('drugRate',[0.5],[x0periodic;ymid]);
>    y=Y(:,2); s=size(y); y05=y(s(1));
```

```
>   [t,Y]=ode23('drugRate',[.5 6],[x05; y05]); y=Y(:,2); s=size(y); y6=y(s(1));
>   if y6 > ymid
>      yleft=ymid;
>   else
>      yright=ymid;
>   end
> end
> y0periodic=ymid
```

The result is that y_0 is about 0.8864. Figure 9.11.4 shows one period of $x(t)$ and $y(t)$ superimposed on the same graph, and Figure 9.11.5 is the parametric plot $(x(t),\ y(t))$. These are produced by the following computer codes. For Figure 9.11.4:

MAPLE

```
> plot({[t,x1(t),t=0..1/2],[t,x2(t),t=1/2..6],[t,y1(t),t=0..1/2],[t,y2(t),t=1/2..6]},color=BLACK);
```

MATLAB

```
> [t,Y]=ode23('drugRate',[0 6],[x0periodic; y0periodic]);
> plot(t,Y)
```

And for Figure 9.11.5:

MAPLE

```
> plot({[x1(t),y1(t),t=0..1/2],[x2(t),y2(t),t=1/2..6]},view=[0..1,0..2],color=BLACK);
```

MATLAB

```
> plot(t,Y); plot(Y(:,1),Y(:,2))
```

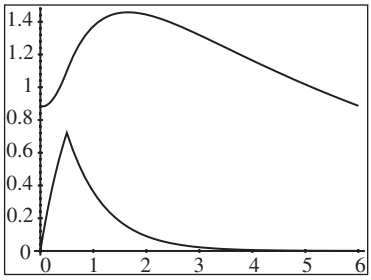


Fig. 9.11.4. Superimposed plots of $x(t)$ (lower) and $y(t)$ (upper).

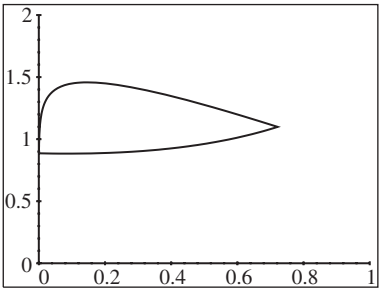


Fig. 9.11.5. Parametric plot $(x(t),\ y(t))$.

This model continues to raise many questions. Because $y(t)$ represents the level of the drug in the circulatory system, we note that the level should be large enough

for the drug to be effective, and but not so large as to cause side effects. The job of the pharmaceutical company is to determine the appropriate level that y should have, and to adjust a and b to maintain that level.

Exercises/Experiments

1. A part of the interest in [13] was to contrast the behaviors of PPA and CPM. CPM has a half-life of one hour in the GI tract and 30 hours in the blood system. This contrast can be made by modifying the code suggested in Section 9.11.
2. With the model of this section, suppose that a and b are as specified for the two drugs. What could be an initial intravenous injection level, x_0, with subsequent equal dose levels as specified and taken orally, so that the periodic steady state is achieved in the first six hours and maintained thereafter?

Questions for Thought and Discussion

1. For what anatomical and molecular reasons do we expect the lead in leaded gasoline to move percutaneously into our bodies?
2. Describe the path of ingested lead from mouth to bone marrow.
3. For what reasons might we expect a person who has ingested lead to become anemic?

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