

PRINCIPLES AND APPLICATIONS IN ENGINEERING SERIES

Edited by

MARTIN L. YARMUSH

MEHMET TONER

ROBERT PLONSEY

JOSEPH D. BRONZINO

Biotechnology for Biomedical Engineers



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Preface

The human genome project has altered the very nature of research and development related to the treatment of disease and, in the process, has revolutionized the field of “biotechnology.” Pioneering work in genomics, for example, has led to the development of sophisticated techniques for determining differential gene-expression patterns (transcriptomics) resulting from genetic makeup, disease state or influence from external factors. This book—*Biotechnology for Biomedical Engineers*—takes the sections most relevant to this important topic from the second edition of the *Biomedical Engineering Handbook* published in 2000. Since it is important for individuals engaged in this field to understand the fundamentals of physiology, this handbook opens with a section on Physiologic Systems, edited by Robert Plonsey, which provides an overview of the major physiologic systems of current interest to biomedical engineers, namely the cardiovascular, endocrine, nervous, visual, auditory, gastrointestinal and respiratory systems. It is important to note that this section is written at an introductory and tutorial level. However, since this book has been prepared for the biomedical engineering community, mathematical descriptions are not avoided.

In the subsequent chapters, the major editors, Drs. Martin Yarmush and Mehmet Toner, have assembled material that covers most topics in biotechnology that might interest the practicing biomedical engineer. During the past two decades, the field of biotechnology in the advent of recombinant DNA technology, monoclonal antibody technology, and new technologies for studying and handling cells and tissues, has gone through a tremendous resurgence in a wide range of applications pertinent to industry, medicine, and science in general. Some of these new ideas, concepts, and technologies are covered in this handbook.

With this in mind, the *Biotechnology for Biomedical Engineers Handbook* presents:

- Approaches and techniques to manipulate genetic materials. This capability, which provides the practitioner with the potential to generate new proteins with improved biochemical and physiochemical properties, has led to the formation of the field of **protein engineering**.
- The field of monoclonal antibody production in terms of its basic technology, diverse applications, and ways that the field of recombinant DNA technology is currently “reshaping” some of the earlier constructs.
- Applications of nucleic acid chemistry, as well as the burgeoning field of antisense technology, with emphasis on basic techniques and potential applications to AIDS and cancer.
- The computational, chemical, and machine tools that are being developed and refined for genome analysis.
- The fundamentals of applied virology in which viral vaccines and viral-mediated gene therapy are the main foci.
- Important aspects of cell structure and function, emphasizing a common approach toward quantitative analysis of cell behavior in order to develop the principles for cell growth and function.

By viewing the world of biotechnology through the use of proteins and nucleic acids and through viruses to cells, today's biomedical engineer will hopefully be prepared to meet the challenge of participating in the greater field of biotechnology.

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Robert Plonsey

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Physiologic Systems

Robert Plonsey
Duke University

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THE CONTENT OF THIS HANDBOOK is devoted to the subject of *biomedical engineering*. We understand biomedical engineering to involve the application of engineering science and technology to problems arising in medicine and biology. In principle, the intersection of each engineering discipline (i.e., electrical, mechanical, chemical, etc.) with each discipline in medicine (i.e., cardiology, pathology, neurology, etc.) or biology (i.e., biochemistry, pharmacology, molecular biology, cell biology, etc.) is a potential area of biomedical engineering application. As such, the discipline of biomedical engineering is potentially very extensive. However, at least to date, only a few of the

afore-mentioned “intersections” contain active areas of research and/or development. The most significant of these are described in this handbook.

While the application of engineering expertise to the life sciences requires an obvious knowledge of contemporary technical theory and its applications, it also demands an adequate knowledge and understanding of relevant medicine and biology. It has been argued that the most challenging part of finding engineering solutions to problems lies in the formulation of the solution in engineering terms. In biomedical engineering, this usually demands a full understanding of the life science substrates as well as the quantitative methodologies.

This section is devoted to an overview of the major physiologic systems of current interest to biomedical engineers, on which their work is based. The overview may contain useful definitions, tables of basic physiologic data, and an introduction to the literature. Obviously these chapters must be extremely brief. However, our goal is an introduction that may enable the reader to clarify some item of interest or to indicate a way to pursue further information. Possibly the reader will find the greatest value in the references to more extensive literature.

This section contains seven chapters, and these describe each of the major organ systems of the human body. Thus we have chapters describing the cardiovascular, endocrine, nervous, visual, auditory, gastrointestinal, and respiratory systems. While each author is writing at an introductory and tutorial level, the audience is assumed to have some technical expertise, and consequently, mathematical descriptions are not avoided. All authors are recognized as experts on the system that they describe, but all are also biomedical engineers.

The authors in this section noted that they would have liked more space but recognized that the main focus of this handbook is on “engineering.” Hopefully, readers will find this introductory section helpful to their understanding of later chapters and, as noted above, to at least provide a starting point for further investigation into the life sciences.

1

An Outline of Cardiovascular Structure and Function

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Because not every cell in the human body is near enough to the environment to easily exchange with it mass (including nutrients, oxygen, carbon dioxide, and the waste products of metabolism), energy (including heat), and momentum, the physiologic system is endowed with a major highway network—organized to make available thousands of miles of access tubing for the transport to and from a different neighborhood (on the order of 10 μm or less) of any given cell whatever it needs to sustain life. This highway network, called the *cardiovascular system*, includes a pumping station, the heart; a working fluid, blood; a complex branching configuration of distributing and collecting pipes and channels, blood vessels; and a sophisticated means for both intrinsic (inherent) and extrinsic (autonomic and endocrine) control.

1.1 The Working Fluid: Blood

Accounting for about $8 \pm 1\%$ of total body weight, averaging 5200 ml, blood is a complex, heterogeneous suspension of formed elements—the *blood cells*, or *hematocytes*—suspended in a continuous, straw-colored fluid called *plasma*. Nominally, the composite fluid has a mass density of $1.057 \pm 0.007 \text{ g/cm}^3$, and it is three to six times as viscous as water. The hematocytes (Table 1.1) include three basic types of cells: red blood cells (erythrocytes, totaling nearly 95% of the formed elements), white blood cells (leukocytes, averaging $<0.15\%$ of all hematocytes), and platelets (thrombocytes, on the order of 5% of all blood cells). Hematocytes are all derived in the active (“red”) bone marrow (about 1500 g) of adults from undifferentiated stem cells called *hemocytoblasts*, and all reach ultimate maturity via a process called *hematocytopenesis*.

The primary function of erythrocytes is to aid in the transport of blood gases—about 30 to 34% (by weight) of each cell consisting of the oxygen- and carbon dioxide-carrying protein hemoglobin (64,000 $\leq \text{MW} \leq 68,000$) and a small portion of the cell containing the enzyme carbonic anhydrase, which catalyzes the reversible formation of carbonic acid from carbon dioxide and water. The primary function of leukocytes is to endow the human body with the ability to identify and dispose of foreign substances such as infectious organisms) that do not belong there—agranulocytes (lymphocytes and monocytes)

TABLE 1.1 Hematocytes

Cell Type	Number Cells per mm ³ Blood*	Corpuscular Diameter (μm)*	Corpuscular Surface Area (μm ²)*	Corpuscular Volume (μm ³)*	Mass Density (g/cm ³)*	Percent Water*	Percent Protein *	Percent Extractives*†
Erythrocytes (red blood cells)	4.2–5.4 × 10 ⁶ ♀ 4.6–6.2 × 10 ⁶ ♂ (5 × 10 ⁶)	6–9 (7.5) Thickness 1.84–2.84 “Neck” 0.81–1.44	120–163 (140)	80–100 (90)	1.089–1.100 (1.098)	64–68 (66)	29–35 (32)	1.6–2.8 (2)
Leukocytes (white blood cells)	4000–11000 (7500)	6–10	300–625	160–450	1.055–1.085	52–60 (56)	30–36 (33)	4–18 (11)
Granulocytes								
Neutrophils:	2–6 × 10 ³ (4875)	8–8.6 (8.3)	422–511 (467)	268–333 (300)	1.075–1.085 (1.080)	—	—	—
55–70% WBC (65%)								
Eosinophils:	45–480 (225)	8–9 (8.5)	422–560 (491)	268–382 (321)	1.075–1.085 (1.080)	—	—	—
1–4% WBC (3%)								
Basophils:	0–113 (75)	7.7–8.5 (8.1)	391–500 (445)	239–321 (278)	1.075–1.085 (1.080)	—	—	—
0–1.5% WBC (1%)								
Agranulocytes								
Lymphocytes:	1000–4800 (1875)	6.75–7.34 (7.06)	300–372 (336)	161–207 (184)	1.055–1.070 (1.063)	—	—	—
20–35% WBC (25%)								
Monocytes:	100–800 (450)	9–9.5 (9.25)	534–624 (579)	382–449 (414)	1.055–1.070 (1.063)	—	—	—
3–8% WBC (6%)								
Thrombocytes (platelets)	(1.4 ♂), 2.14 (♀)–5 × 10 ⁵	2–4 (3) Thickness 0.9–1.3	16–35 (25)	5–10 (7.5)	1.04–1.06 (1.05)	60–68 (64)	32–40 (36)	Neg.
(2.675 × 10 ⁵)								

*Normal physiologic range, with “typical” value in parentheses.
†Extractives include mostly minerals (ash), carbohydrates, and fats (lipids).

essentially doing the “identifying” and granulocytes (neutrophils, basophils, and eosinophils) essentially doing the “disposing.” The primary function of platelets is to participate in the blood-clotting process.

Removal of all hematocytes from blood centrifugation or other separating techniques leaves behind the aqueous (91% water by weight, 94.8% water by volume), saline (0.15 N) suspending medium called *plasma*—which has an average mass density of $1.035 \pm 0.005 \text{ g/cm}^3$ and a viscosity $1\frac{1}{2}$ to 2 times that of water. Some 6.5 to 8% by weight of plasma consists of the plasma proteins, of which there are three major types—albumin, the globulins, and fibrinogen—and several of lesser prominence (Table 1.2).

TABLE 1.2 Plasma

Constituent	Concentration Range (mg/dl plasma)	Typical Plasma Value (mg/dl)	Molecular Weight Range	Typical Value	Typical Size (nm)
Total protein, 7% by weight	6400–8300	7245	21,000–1,200,000	—	—
Albumin (56% TP)	2800–5600	4057	66,500–69,000	69,000	15×4
α_1 -Globulin (5.5% TP)	300–600	400	21,000–435,000	60,000	5–12
α_2 -Globulin (7.5% TP)	400–900	542	100,000–725,000	200,000	50–500
β -Globulin (13% TP)	500–1230	942	90,000–1,200,000	100,000	18–50
γ -Globulin (12% TP)	500–1800	869	150,000–196,000	150,000	23×4
Fibrinogen (4% TP)	150–470	290	330,000–450,000	390,000	$(50-60) \times (3-8)$
Other (2% TP)	70–210	145	70,000–1,000,000	200,000	$(15-25) \times (2-6)$
Inorganic ash, 0.95% by weight	930–1140	983	20–100	—	—
Sodium	300–340	325	—	22.98977	(Radius) 0.102 (Na ⁺)
Potassium	13–21	17	—	39.09800	0.138 (K ⁺)
Calcium	8.4–11.0	10	—	40.08000	0.099 (Ca ²⁺)
Magnesium	1.5–3.0	2	—	24.30500	0.072 (Mg ²⁺)
Chloride	336–390	369	—	35.45300	0.181 (Cl ⁻)
Bicarbonate	110–240	175	—	61.01710	0.163 (HCO ₃ ⁻)
Phosphate	2.7–4.5	3.6	—	95.97926	0.210 (HPO ₄ ²⁻)
Sulfate	0.5–1.5	1.0	—	96.05760	0.230 (SO ₄ ²⁻)
Other	0–100	80.4	20–100	—	0.1–0.3
Lipids (fats), 0.80% by weight	541–1000	828	44,000–3,200,000	= Lipoproteins	Up to 200 or more
Cholesterol (34% TL)	12–105 “free” 72–259 esterified, 84–364 “total”	59 224 283	386.67	Contained mostly in intermediate to LDL β -lipoproteins; higher in women	
Phospholipid (35% TL)	150–331	292	690–1010	Contained mainly in HDL to VLDL α_1 -lipoproteins	
Triglyceride (26% TL)	65–240	215	400–1370	Contained mainly in VLDL α_2 -lipoproteins and chylomicrons	
Other (5% TL)	0–80	38	280–1500	Fat-soluble vitamins, prostaglandins, fatty acids	
Extractives, 0.25% by weight	200–500	259	—	—	—
Glucose	60–120, fasting	90	—	180.1572	0.86 D
Urea	20–30	25	—	60.0554	0.36 D
Carbohydrate	60–105	83	180.16–342.3	—	0.74–0.108 D
Other	11–111	61	—	—	—

The primary functions of albumin are to help maintain the osmotic (oncotic) transmural pressure differential that ensures proper mass exchange between blood and interstitial fluid at the capillary level and to serve as a transport carrier molecule for several hormones and other small biochemical constituents (such as some metal ions). The primary function of the globulin class of proteins is to act as transport carrier molecules (mostly of the α and β class) for large biochemical substances, such as fats (lipoproteins) and certain carbohydrates (mucopolysaccharides and glycoproteins) and heavy metals (mineraloproteins), and to work together with leukocytes in the body's immune system. The latter function is primarily the responsibility of the γ class of immunoglobulins, which have antibody activity. The primary function of fibrinogen is to work with thrombocytes in the formation of a blood clot—a process also aided by one of the most abundant of the lesser proteins, prothrombin (MW 62,000).

Of the remaining 2% or so (by weight) of plasma, just under half (0.95%, or 983 mg/dl plasma) consists of minerals (inorganic ash), trace elements, and electrolytes, mostly the cations sodium, potassium, calcium, and magnesium and the anions chlorine, bicarbonate, phosphate, and sulfate—the latter three helping as buffers to maintain the fluid at a slightly alkaline pH between 7.35 and 7.45 (average 7.4). What is left, about 1087 mg of material per deciliter of plasma, includes: (1) mainly (0.8% by weight) three major types of fat, i.e., cholesterol (in a free and esterified form), phospholipid (a major ingredient of cell membranes), and triglyceride, with lesser amounts of the fat-soluble vitamins (A, D, E, and K), free fatty acids, and other lipids, and (2) “extractives” (0.25% by weight), of which about two-thirds includes glucose and other forms of carbohydrate, the remainder consisting of the water-soluble vitamins (B-complex and C), certain enzymes, nonnitrogenous and nitrogenous waste products of metabolism (including urea, creatine, and creatinine), and many smaller amounts of other biochemical constituents—the list seeming virtually endless.

Removal from blood of all hematocytes and the protein fibrinogen (by allowing the fluid to completely clot before centrifuging) leaves behind a clear fluid called *serum*, which has a density of about $1.018 \pm 0.003 \text{ g/cm}^3$ and a viscosity up to $1\frac{1}{2}$ times that of water. A glimpse of Tables 1.1 and 1.2, together with the very brief summary presented above, nevertheless gives the reader an immediate appreciation for why blood is often referred to as the “river of life.” This river is made to flow through the vascular piping network by two central pumping stations arranged in series: the left and right sides of the human heart.

1.2 The Pumping Station: The Heart

Barely the size of the clenched fist of the individual in whom it resides—an inverted, conically shaped, hollow muscular organ measuring 12 to 13 cm from base (top) to apex (bottom) and 7 to 8 cm at its widest point and weighing just under 0.75 lb (about 0.474% of the individual's body weight, or some 325 g)—the human heart occupies a small region between the third and sixth ribs in the central portion of the thoracic cavity of the body. It rests on the diaphragm, between the lower part of the two lungs, its base-to-apex axis leaning mostly toward the left side of the body and slightly forward. The heart is divided by a tough muscular wall—the interatrial-interventricular septum—into a somewhat crescent-shaped right side and cylindrically shaped left side (Fig. 1.1), each being one self-contained pumping station, but the two being connected in series. The left side of the heart drives oxygen-rich blood through the aortic semilunar outlet valve into the *systemic circulation*, which carries the fluid to within a differential neighborhood of each cell in the body—from which it returns to the right side of the heart low in oxygen and rich in carbon dioxide. The right side of the heart then drives this oxygen-poor blood through the pulmonary semilunar (pulmonic) outlet valve into the *pulmonary circulation*, which carries the fluid to the lungs—where its oxygen supply is replenished and its carbon dioxide content is purged before it returns to the left side of the heart to begin the cycle all over again. Because of the anatomic proximity of the heart to the lungs, the right side of the heart does not have to work very hard to drive blood through the pulmonary circulation, so it functions as a low-pressure ($P = 40 \text{ mmHg}$ gauge) pump compared with the left side of the heart, which does most of its work at a high pressure (up to 140 mmHg gauge or more) to drive blood through the entire systemic circulation to the furthest extremes of the organism.

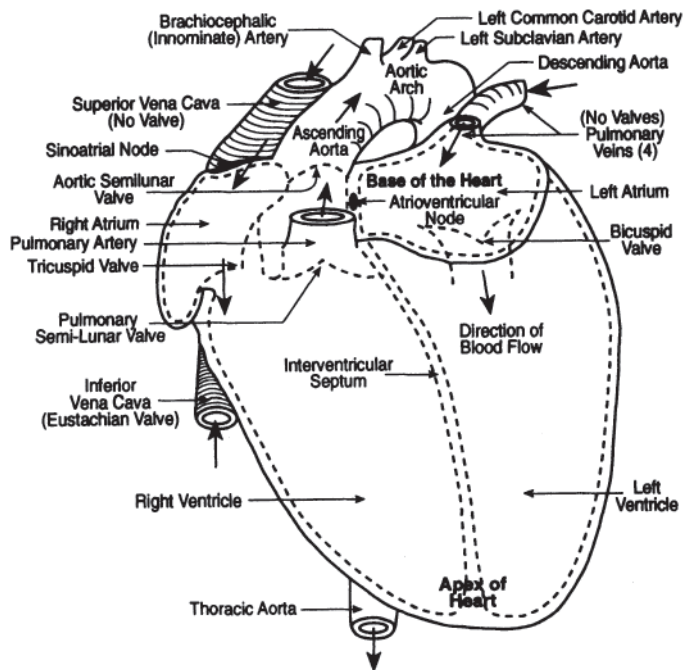


FIGURE 1.1. Anterior view of the human heart showing the four chambers, the inlet and outlet valves, the inlet and outlet major blood vessels, the wall separating the right side from the left side, and the two cardiac pacing centers—the sinoatrial node and the atrioventricular node. Boldface arrows show the direction of flow through the heart chambers, the valves, and the major vessels.

Each cardiac (heart) pump is further divided into two chambers: a small upper receiving chamber, or atrium (auricle), separated by a one-way valve from a lower discharging chamber, or ventricle, which is about twice the size of its corresponding atrium. In order of size, the somewhat spherically shaped left atrium is the smallest chamber—holding about 45 ml of blood (at rest), operating at pressures on the order of 0 to 25 mmHg gauge, and having a wall thickness of about 3 mm. The pouch-shaped right atrium is next (63 ml of blood, 0 to 10 mmHg gauge of pressure, 2-mm wall thickness), followed by the conical/cylindrically shaped left ventricle (100 ml of blood, up to 140 mmHg gauge of pressure, variable wall thickness up to 12 mm) and the crescent-shaped right ventricle (about 130 ml of blood, up to 40 mmHg gauge of pressure, and a wall thickness on the order of one-third that of the left ventricle, up to about 4 mm). All together, then, the heart chambers collectively have a capacity of some 325 to 350 ml, or about 6.5% of the total blood volume in a “typical” individual—but these values are nominal, since the organ alternately fills and expands, contracts, and then empties as it generates a *cardiac output*.

During the 480-ms or so filling phase—diastole—of the average 750-ms cardiac cycle, the inlet valves of the two ventricles (3.8-cm-diameter tricuspid valve from right atrium to right ventricle; 3.1-cm-diameter bicuspid or mitral valve from left atrium to left ventricle) are open, and the outlet valves (2.4-cm-diameter pulmonary valve and 2.25-cm-diameter aortic semilunar valve, respectively) are closed—the heart ultimately expanding to its end-diastolic-volume (EDV), which is on the order of 140 ml of blood for the left ventricle. During the 270-ms emptying phase—systole—electrically induced vigorous contraction of cardiac muscle drives the intraventricular pressure up, forcing the one-way inlet valves closed and the unidirectional outlet valves open as the heart contracts to its end-systolic-volume (ESV), which is typically on the order of 70 ml of blood for the left ventricle. Thus the ventricles normally empty about half their contained volume with each heart beat, the remainder being termed the *cardiac reserve volume*. More generally, the difference between the *actual* EDV and the *actual* ESV, called the *stroke volume* (SV), is the volume of blood expelled from the heart during each systolic interval, and the ratio

of SV to EDV is called the *cardiac ejection fraction*, or *ejection ratio* (0.5 to 0.75 is normal, 0.4 to 0.5 signifies mild cardiac damage, 0.25 to 0.40 implies moderate heart damage, and <0.25 warns of severe damage to the heart's pumping ability). If the stroke volume is multiplied by the number of systolic intervals per minute, or heart (HR), one obtains the total cardiac output (CO):

$$\text{CO} = \text{HR} \times (\text{EDV} - \text{ESV}). \quad (1.1)$$

Dawson [1991] has suggested that the cardiac output (in milliliters per minute) is proportional to the weight W (in kilograms) of an individual according to the equation,

$$\text{CO} = 224W^{3/4}, \quad (1.2)$$

and that “normal” heart rate obeys very closely the relation,

$$\text{HR} = 229W^{-1/4}. \quad (1.3)$$

For a “typical” 68.7-kg individual (blood volume=5200 ml), Equations (1.1), (1.2), and (1.3) yield $\text{CO}=5345$ ml/min, $\text{HR}=80$ beats/min (cardiac cycle period=754 ms) and $\text{SV}=\text{CO}/\text{HR}=224W^{3/4}/229W^{-1/4}=0.978W=67.2$ ml/beat, which are very reasonable values. Furthermore, assuming this individual lives about 75 years, his or her heart will have cycled over 3.1536 billion times, pumping a total of 0.2107 billion liters of blood (55.665 million gallons, or 8134 quarts per day)—all of it emptying into the circulatory pathways that constitute the vascular system.

1.3 The Piping Network: Blood Vessels

The vascular system is divided by a microscopic capillary network into an upstream, high-pressure, efferent arterial side (Table 1.3)—consisting of relatively thick-walled, viscoelastic tubes that carry blood away from the heart—and a downstream, low-pressure, afferent venous side (Table 1.4)—consisting of correspondingly thinner (but having a larger caliber) elastic conduits that return blood back to the heart. Except for their differences in thickness, the walls of the largest arteries and veins consist of the same three distinct, well-defined, and well-developed layers. From innermost to outermost, these layers are (1) the thinnest *tunica intima*, a continuous lining (the vascular endothelium) consisting of a single layer of simple squamous (thin, sheetlike) endothelial cells “glued” together by a polysaccharide (sugar) intercellular matrix, surrounded by a thin layer of subendothelial connective tissue interlaced with a number of circularly arranged elastic fibers to form the subendothelium, and separated from the next adjacent wall layer by a thick elastic band called the *internal elastic lamina*, (2) the thickest *tunica media*, composed of numerous circularly arranged elastic fibers, especially prevalent in the largest blood vessels on the arterial side (allowing them to expand during systole and to recoil passively during diastole), a significant amount of smooth muscle cells arranged in spiraling layers around the vessel wall, especially prevalent in medium-sized arteries and arterioles (allowing them to function as control points for blood distribution), and some interlacing collagenous connective tissue, elastic fibers, and intercellular mucopolysaccharide substance (extractives), all separated from the next adjacent wall layer by another thick elastic band called the *external elastic lamina*, and (3) the medium-sized *tunica adventitia*, an outer vascular sheath consisting entirely of connective tissue.

The largest blood vessels, such as the aorta, the pulmonary artery, the pulmonary veins, and others, have such thick walls that they require a separate network of tiny blood vessels—the vasa vasorum—just to service the vascular tissue itself. As one moves toward the capillaries from the arterial side (see Table 1.3), the vascular wall keeps thinning, as if it were shedding 15- μm -thick, onion-peel-like concentric layers, and while the percentage of water in the vessel wall stays relatively constant at 70% (by weight), the ratio of elastin to collagen decreases (actually reverses)—from 3:2 in large arteries

TABLE 1.3 Arterial System*

Blood Vessel Type	(Systemic) Typical Number	Internal Diameter Range	Length Range†	Wall Thickness	Systemic Volume	(Pulmonary) Typical Number	Pulmonary Volume
Aorta	1	1.0–3.0 cm	30–65 cm	2–3 mm	156 ml	—	—
Pulmonary artery	—	2.5–3.1 cm	6–9 cm	2–3 cm	—	1	52 ml
Wall morphology: Complete tunica adventitia, external elastic lamina, tunica media, internal elastic lamina, tunica intima, subendothelium, endothelium, and vasa vasorum vascular supply							
Main branches (Along with the aorta and pulmonary artery, the largest, most well-developed of all blood vessels)	32	5 mm–2.25 cm	3.3–6 cm	≈2 mm	83.2 ml	6	41.6 ml
Large arteries (A well-developed tunica adventitia and vasa vasorum, although wall layers are gradually thinning)	288	4.0–5.0 mm	1.4–2.8 mm	≈1 mm	104 ml	64	23.5 ml
Medium arteries	1152	2.5–4.0 mm	1.0–2.2 cm	≈0.75 mm	117 ml	144	7.3 ml
Small arteries	3456	1.0–2.5 mm	0.6–1.7 cm	≈0.50 mm	104 ml	432	5.7 ml
Tributaries (Well-developed tunica media and external elastic lamina, but tunica adventitia virtually nonexistent)	20,736	0.5–1.0 mm	0.3–1.3 cm	≈0.25 mm	91 ml	5184	7.3 ml
Small rami	82,944	250–500 μm	0.2–0.8 cm	≈125 μm	57.2 ml	11,664	2.3 ml
Terminal branches	497,664	100–250 μm	1.0–6.0 mm	≈60 μm	52 ml	139,968	3.0 ml
(A well-developed endothelium, subendothelium, and internal elastic lamina, plus about two to three 15-μm-thick concentric layers forming just a very thin tunica media; no external elastic lamina)							
Arterioles	18,579,456	25–100 μm	0.2–3.8 mm	≈20–30 μm	52 ml	4,094,064	2.3 ml
Wall morphology: More than one smooth muscle layer (with nerve association in the outermost muscle layer), a well-developed internal elastic lamina; gradually thinning in 25- to 50-μm vessels to a single layer of smooth muscle tissue, connective tissue, and scant supporting tissue.							
Metarterioles	238,878,720	10–25 μm	0.1–1.8 mm	≈5–15 μm	41.6 ml	157,306,536	4.0 ml
(Well-developed subendothelium; discontinuous contractile muscle elements; one layer of connective tissue)							
Capillaries	16,124,431,360	3.5–10 μm	0.5–1.1 mm	≈0.5–1 μm	260 ml	3,218,406,696	104 ml
(Simple endothelial tubes devoid of smooth muscle tissue; one-cell-layer-thick walls)							

*Values are approximate for a 68.7-kg individual having a total blood volume of 5200 ml.
†Average uninterrupted distance between branch origins (except aorta and pulmonary artery, which are total length).

TABLE 1.4 Venous System

Blood Vessel Type	(Systemic) Typical Number	Internal Diameter Range	Length Range	Wall Thickness	Systemic Volume	(Pulmonary) Typical Number	Pulmonary Volume
Postcapillary venules (Wall consists of thin endothelium exhibiting occasional pericytes (pericapillary connective tissue cells) that increase in number as the vessel lumen gradually increases)	4,408,161,734	8–30 μ m	0.1–0.6 mm	1.0–5.0 μ m	166.7 ml	306,110,016	10.4 ml
Collecting venules (One complete layer of pericytes, one complete layer of veil cells (veil-like cells forming a thin membrane), occasional primitive smooth muscle tissue fibers that increase in number with vessel size)	160,444,500	30–50 μ m	0.1–0.8 mm	5.0–10 μ m	161.3 ml	8,503,056	1.2 ml
Muscular venules (Relatively thick wall of smooth muscle tissue)	32,088,900	50–100 μ m	0.2–1.0 mm	10–25 μ m	141.8 ml	3,779,136	3.7 ml
Small collecting veins (Prominent tunica media of continuous layers of smooth muscle cells)	10,241,508	100–200 μ m	0.5–3.2 mm	\approx 30 μ m	329.6 ml	419,904	6.7 ml
Terminal branches (A well-developed endothelium, subendothelium, and internal elastic lamina; well-developed tunica media but fewer elastic fibers than corresponding arteries and much thinner walls)	496,900	200–600 μ m	1.0–6.0 mm	30–150 μ m	206.6 ml	34,992	5.2 ml
Small veins	19,968	600 μ m–1.1 mm	2.0–9.0 mm	\approx 0.25 mm	63.5 ml	17,280	44.9 ml
Medium veins	512	1–5 mm	1–2 cm	\approx 0.50 mm	67.0 ml	144	22.0 ml
Large veins (Well-developed wall layers comparable to large arteries but about 25% thinner)	256	5–9 mm	1.4–3.7 cm	\approx 0.75 mm	476.1 ml	48	29.5 ml
Main branches (Along with the vena cava and pulmonary veins, the largest, most well-developed of all blood vessels)	224	9.0 mm–2.0 cm	2.0–10 cm	\approx 1.00 mm	1538.1 ml	16	39.4 ml
Vena cava	1	2.0–3.5 cm	20–50 cm	\approx 1.50 mm	125.3 ml	—	—
Pulmonary veins	—	1.7–2.5 cm	5–8 cm	\approx 1.50 mm	—	4	52 ml
Wall morphology: Essentially the same as comparable major arteries but a much thinner tunica intima, a much thinner tunica media, and a somewhat thicker tunica adventitia; contains a vasa vasorum							

Total systemic blood volume: 4394 ml—84.5% of total blood volume; 19.5% in arteries (~3.2 large:small), 5.9% in capillaries, 74.6% in veins (~3.1 large:small); 63% of volume is in vessels greater than 1 mm internal diameter

Total pulmonary blood volume: 468 ml—9.0% of total blood volume; 31.8% in arteries, 22.2% in capillaries, 46% in veins; 58.3% of volume is in vessels greater than 1 mm internal diameter; remainder of blood in heart, about 338 ml (6.5% of total blood volume)

(9% elastin, 6% collagen, by weight) to 1:2 in small tributaries (5% elastin, 10% collagen)—and the amount of smooth muscle tissue increases from 7.5% by weight of large arteries (the remaining 7.5% consisting of various extractives) to 15% in small tributaries. By the time one reaches the capillaries, one encounters single-cell-thick endothelial tubes—devoid of any smooth muscle tissue, elastin, or collagen—downstream of which the vascular wall gradually “reassembles itself,” layer by layer, as it directs blood back to the heart through the venous system (Table 1.4).

Blood vessel structure is directly related to function. The thick-walled large arteries and main *distributing branches* are designed to withstand the pulsating 80-to-130-mmHg blood pressures that they must endure. The smaller elastic *conducting vessels* need only operate under steadier blood pressures in the range 70 to 90 mmHg, but they must be thin enough to penetrate and course through organs without unduly disturbing the anatomic integrity of the mass involved. Controlling arterioles operate at blood pressures between 45 and 70 mmHg but are heavily endowed with smooth muscle tissue (hence their referred to as *muscular vessels*) so that they may be actively shut down when flow to the capillary bed they service is to be restricted (for whatever reason), and the smallest capillary *resistance vessels* (which operate at blood pressures on the order of 10 to 45 mmHg) are designed to optimize conditions for transport to occur between blood and the surrounding interstitial fluid. Traveling back up the venous side, one encounters relatively steady blood pressures continuously decreasing from around 30 mmHg all the way down to near zero, so these vessels can be thin-walled without disease consequence. However, the low blood pressure, slower, steady (time-dependent) flow, thin walls, and larger caliber that characterize the venous system cause blood to tend to “pool” in veins, allowing them to act somewhat like reservoirs. It is not surprising, then, that at any given instant, one normally finds about two-thirds of the total human blood volume residing in the venous system, the remaining one-third being divided among the heart (6.5%), the microcirculation (7% in systemic and pulmonary capillaries), and the arterial system (19.5 to 20%).

In a global sense, then, one can think of the human cardiovascular system—using an electrical analogy—as a voltage source (the heart), two capacitors (a large venous system and a smaller arterial system), and a resistor (the microcirculation taken as a whole). Blood flow and the dynamics of the system represent electrical inductance (inertia), and useful engineering approximations can be derived from such a simple model. The cardiovascular system is designed to bring blood to within a capillary size of each and every one of the more than 10^{14} cells of the body—but *which* cells receive blood at any given time, *how much* blood they get, the *composition* of the fluid coursing by them, and related physiologic considerations are all matters that are not left up to chance.

1.4 Cardiovascular Control

Blood flows through organs and tissues either to nourish and sanitize them or to be itself processed in some sense—e.g., to be oxygenated (pulmonary circulation), stocked with nutrients (splanchnic circulation), dialyzed (renal circulation), cooled (cutaneous circulation), filtered of dilapidated red blood cells (splenic circulation), and so on. Thus any given vascular network normally receives blood according to the metabolic needs of the region it perfuses and/or the function of that region as a blood treatment plant and/or thermoregulatory pathway. However, it is not feasible to expect that our physiologic transport system can be “all things to all cells all of the time”—especially when resources are scarce and/or time is a factor. Thus the distribution of blood is further prioritized according to three basic criteria: (1) how essential the perfused region is to the maintenance of life itself (e.g., we can survive without an arm, a leg, a stomach, or even a large portion of our small intestine but not without a brain, a heart, and at least one functioning kidney and lung), (2) how essential the perfused region is in allowing the organism to respond to a life-threatening situation (e.g., digesting a meal is among the least of the body’s concerns in a “fight-or-flight” circumstance), and (3) how well the perfused region can function and survive on a decreased supply of blood (e.g., some tissues—like striated skeletal and smooth muscle—have significant anaerobic capability; others—like several forms of connective tissue—can function quite effectively at a significantly decreased metabolic rate when necessary; some organs—like the liver—are larger than they