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Preface to the Second Edition

THE LAST DECADE has seen rapid advances in knowledge of every aspect of respiratory and pulmonary disorders: early diagnosis of emphysema and diseases of small airways, management of respiratory distress syndrome of the newborn and "shock lung" of adults, regulation of breathing in patients with chronic hypoxia and those whose carotid bodies have been removed, the role of vagal reflexes from the lungs of unanesthetized man, the effect of gravity on airways and pulmonary circulation, new methods to detect nonmatching alveolar ventilation and pulmonary capillary blood flow, the effect of diphosphoglycerate (DPG) on the uptake and release of oxygen by hemoglobin, evaluation of acid-base disorders, defense mechanisms of the lung, new functions of the lungs and pulmonary circulation, biochemistry of the lungs, maturation of lungs from the fetus to the newborn to the adult and scanning electron microscopy to provide three-dimensional, detailed pictures of airway and lung surfaces. The last decade has also seen the general acceptance of the respiratory intensive care unit for newborn children and adults as a place where new knowledge is continuously applied to saving lives. In addition, it has seen the beginnings of the artificial lung and pulmonary transplantation, which to be clinically useful, still require intensive research on basic biological mechanisms.

The last decade has seen a revolution in pulmonary disease as a specialty: the emergence of strong research and teaching groups in pulmonary disease in American medical schools, the support of research and training in pulmonary disease by the National Heart Institute that in 1969 became the National Heart *and Lung* Institute and the recognition, at last, in 1973, by the old National Tuberculosis Association that it is, in fact, the American Lung Association. Of special significance has been the realization that, to a greater degree than in any other specialty, the finest clinical practice of pulmonary and respiratory disease requires a thorough knowlege of the sciences basic to this specialty. The medical student may continue to question the "relevance" of science in his medical education until he has become a physician responsible for a newborn or adult respiratory intensive care unit or a special pulmonary diagnostic laboratory, when he suddenly realizes the unity of basic sciences and clinical practice—that he cannot make complete diagnoses and correct decisions about treatment without knowing pulmonary and respiratory physiology, pharmacology and biochemistry. He also learns quickly that few of his patients oblige him by presenting an illness that can be managed by rote. He then realizes that his earlier philosophy of anti-intellectualism has "done him in" and that he needs something more than compassion to save the lives of his patients with pulmonary insufficiency and respiratory

failure. He should also realize that the next decade will see another revolution in understanding, diagnosis and treatment and that he will need a good scientific base to understand and evaluate what is ahead.

The explosion of new knowledge and its application has resulted in revision of all chapters of the first edition of this volume, the extensive revision of ten of these, complete revision of two and addition of two new chapters (Defense Mechanisms of the Lung and Nonrespiratory Functions of the Lung). The first edition contained 111 figures. The second edition contains 142; of these, 65 are new and another 17 have been redrawn or revised.

I express my appreciation to Helen Gee Jeung who drew all of the original illustrations, to colleagues and publishers who permitted me to use their published illustrations, and to the following who provided unusually fine unpublished illustrations to use in this edition: John Clements, Gordon Gamsu, Alain Junod, Donald M. McDonald, Abraham Rudolph, John Severinghaus, Una Smith, Norman Staub and Judy Strum. I also acknowledge the generous advice and criticism of William Briscoe, John Clements, Robert Forster, Warren Gold and Abraham Rudolph with several parts of the text.

J. H. C.

Preface to the First Edition

SOME BOOKS for medical students seem to be written for their professors, for research specialists, for book reviewers—or for all three. This one is really intended for students of medicine—whether they are in medical school, in residency training or in the practice of medicine. Some parts of this book may seem to negate this statement, but not if the views that I and many others hold on the aims of medical education are accepted; these parts are included to show how physiological evidence is obtained, analyzed and evaluated; how conclusions are drawn; how hypotheses turn into concepts; how new concepts replace the previously accepted ones; how difficult and complex all of this is; how little we know "for sure" and how much remains to be learned.

Most of the text is a synthesis of what is currently known of the physiology of respiration that may be of direct help or interest to a physician on this planet. It is *not* a revision of *The Lung: Clinical Physiology and Pulmonary Function Tests* by Comroe, Forster, DuBois, Briscoe and Carlsen; its scope is far broader—from the regulation of ventilation to tissue gas exchange. It does, of course, include sections on pulmonary function, but these are placed in proper perspective in relation to a much larger subject.

There are few direct references in the text to the original publications of the many scientists who are responsible for modern respiratory physiology, and the bibliography contains only selected references. Further, because of the nature and size of this volume, some aspects of respiratory physiology have been omitted from it. I believe this is justified because of the publication in 1964 and 1965 of Section 3 of the monumental reference series, *The Handbook of Physiology;* in two of its many volumes are more than 100,000 square inches of text devoted to the Physiology of Respiration, compared to a mere 10,000 in this volume.

I express my appreciation to the many colleagues and publishers who permitted me to reproduce illustrations and to the following, who provided me with unusually fine unpublished illustrations to include in this volume: Robert Byck, Michel Campiche, John Clements, Abraham Guz, Julien Hoffman, Averill Liebow, Robert Mitchell, Lorraine Mortimer, Sergei Sorokin and William Tooley. I acknowledge also the generous assistance of Moran Campbell and Jack Howell with several parts of the text, and the artistry of Helen Gee, who drew all of the original illustrations.

I welcome suggestions for additional sections if accompanied by suggestions for deletions of an equal amount of material.

JULIUS H. COMROE, JR.

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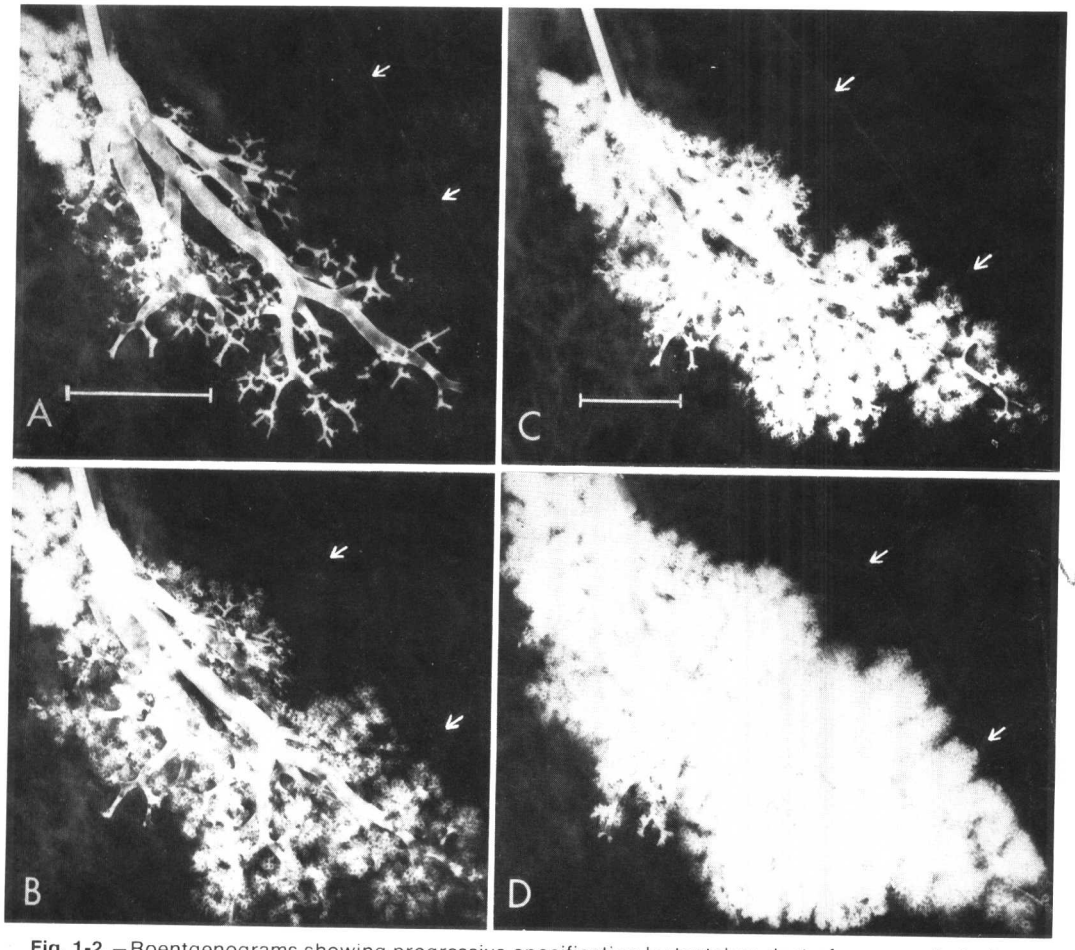

Fig. 1-2. – Roentgenograms showing progressive opacification by tantalum dust of a segment of a human bronchial tree distal to a wedged catheter. Initially, **A,** mainly nonrespiratory bronchioles are visible with some early filling of acini, producing stippling and rosettes. After further opacification, **B** to **D,** the mosaic of more spherical, superimposed but distinct acini is visible. *Arrows* indicate the pleural surface. Marker in **A** represents 2.2 cm in **A, B** and **D**; that in **C** represents 1.8 cm. (From Gamsu, G., *et al.*: Invest. Radiol. 6:171, 1971.)

ing that it lives in water almost completely saturated with air at 1 atmosphere of pressure.

Some larger organisms that live in air (certain insects) do get enough O_2 by diffusion alone, but they have a special system of air tubes (tracheae or spiracles) that pipe air directly to many regions of the body, so that the distances that O_2 must diffuse to reach tissue cells are short.

Large animals, including man, make use of two systems: (1) a blood circulatory system to carry whatever is necessary to and from the tissue cells, with the help of a remarkable chemical, hemoglobin, which insures the transport of large quantities of O_2 and CO_2, and (2) a respiratory system, a gas exchanger, to load the blood with O_2 and remove excess CO_2. In fish, blood flows through the gill vessels and extracts O_2 from water flowing around them. In man, the respiratory surfaces are folded within the body to prevent drying of the delicate membranes; air saturated with water vapor is drawn into intimate

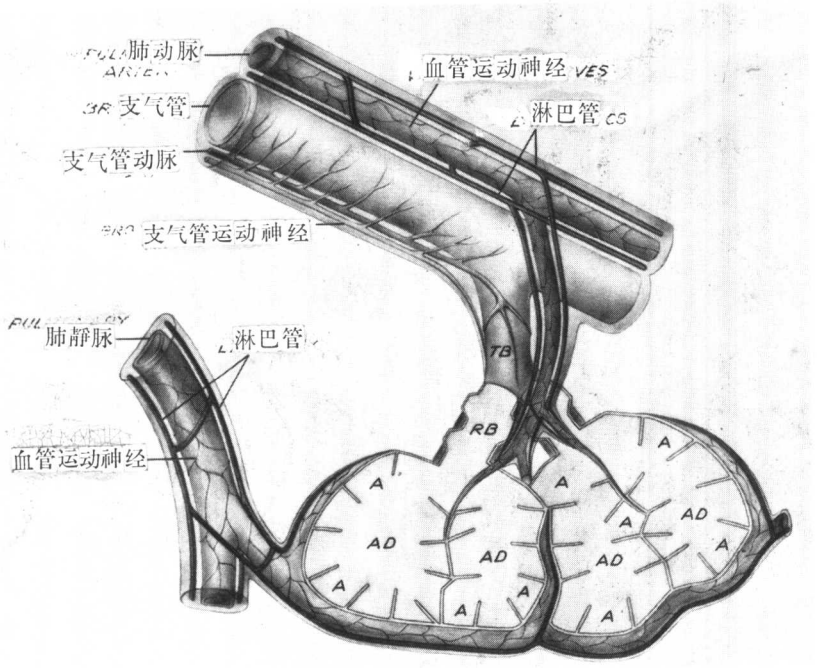

Fig. 1-3. – Lung model showing arrangement of blood and air tubes to terminal air units. Note the relations of the bronchial blood supply, lymphatics and motor innervation, insofar as they are known. Possibilities for selective interactions that regulate local ventilation to local blood flow become apparent in this model. *A* = anatomic alveolus; *AD* = alveolar ducts; *RB* = respiratory bronchiole; *TB* = terminal bronchiole. (From Staub, N. C., in Gray, T. C., and Nunn, J. F. [eds.]: *General Anesthesia* [3d ed.: London, Butterworth & Company, Ltd. 1971], vol. 1, chapter 5.)

contact with the blood flowing through the pulmonary capillaries, and gases are exchanged.

These two systems cooperate to supply the needs of the tissues. One system supplies air; the other supplies blood. Their ultimate purpose is the transfer of gases between air and all tissue cells. The respiratory system uses an air pump, which draws fresh air through air tubes to small air sacs (alveoli) that have very thin membranes. The circulatory system uses a blood pump, which drives the whole output of the heart through fine, thin-walled blood tubes (capillaries) surrounding the alveoli.

The respiratory system is sometimes oversimplified so that it looks like Figure 1-1, which shows that there are 2 main parts to the system: (1) a conducting airway, where practically no gas is exchanged, and (2) alveoli, where large amounts of O_2 and CO_2 are rapidly exchanged. But, in reality, the respiratory system is a very complex distributing system. It starts as 2 nasal tubes (sometimes a third tube, the mouth, is also used), and then becomes one, the trachea. The trachea subdivides into 2 main branches, the right and left bronchi, and each of these divides into 2 more, and each of these usually into 2 more. In all, there are 20–23 subdivisions. A simple calculation shows that 20 divisions of this type produce about a million terminal tubes. At the end of each are numerous blind pouches, the alveoli; here gas exchange occurs (Fig. 1-2). There are about 300 million of these in the 2 lungs of man; their diameter varies from 75 to 300 μ. Some are very close to the center of the lung (the hilum) and some are at the apex or base of the lung, as much as 20–30 cm away from

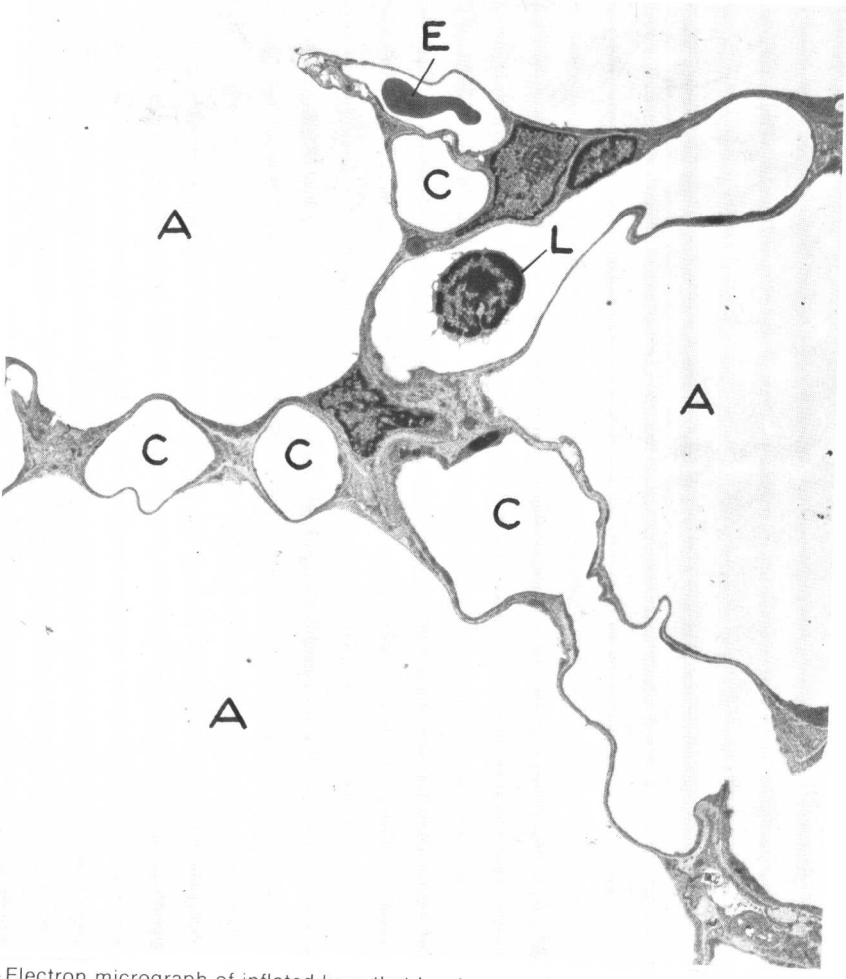

Fig. 1-4.—Electron micrograph of inflated lung that has been perfused with glutaraldehyde fixative. Most capillaries (*C*) are free of blood cells, but one of them contains an erythrocyte (*E*), and another contains a lymphocyte (*L*). Capillary endothelium, basement membrane and alveolar epithelium separate gas in alveoli (*A*) from blood in capillaries. Rat. ×2,000. (Courtesy of Dr. Judy Strum.)

the hilum. Figure 1-3 shows a terminal unit and its alveoli schematically; Figure 1-4 is an electron micrograph of alveoli and their capillaries. To distribute the proper amount of fresh air almost simultaneously to 300 million alveoli of varying sizes through 1 million tubes of varying lengths and diameters requires a remarkable engineering design. Further, since the air in the conducting tubes does not participate in gas exchange, the internal diameter of the tubes must be small (to minimize the volume of wasted air), but not so small that the respiratory pump must do excessive work against friction in moving air through them.

Another remarkable engineering feat provides a vast and extremely thin surface for the transfer of gases between air and blood (Fig. 1-4). Man at rest requires a transfer of only 200–250 ml of O_2/minute, but during maximal exercise he may need more than 20 times this amount—up to 5,500 ml. The surface area of the membrane available for this transfer is huge—about 70 m^2, or 40 times the surface area of the body; the membrane is less than 0.1 μ thick.

The system for supplying blood is often simplified so that it looks like Figure 1-5, but it is as remarkable and complex as the respiratory system. The pump—the right ventricle—drives venous blood into 1 large tube, the pulmonary trunk. This divides and subdivides (Figs. 1-6 and 1-7) until ultimately blood flows through millions of short, thin-walled capillaries surrounding the alveoli. The surface area of this capillary bed is about 70 m^2, the thickness of each capillary wall is less than 0.1 μ and the diameter of each vessel is about 10–14 μ. Yet the resistance to flow through the whole bed is so low that 5–10 L of blood can flow through it each minute with a driving pressure of less than 10 mm Hg. The pump has a wide range. It can push 4 L/minute through the capillaries in man at rest, but as much as 30–40 L/minute when he exercises maximally.

The air and blood pumps are constructed quite differently. The blood is driven by a muscular pump, the right ventricle, which pushes blood in one direction; the tricuspid valves prevent backflow into the right atrium during systole, and the pulmonic valves prevent backflow into the right ventricle during diastole. Blood flows through a conducting system (pulmonary arteries) to the exchange system (capillaries) and a collecting system (pulmonary veins) into a second pump (the left ventricle) for distribution to body cells.

The air pump differs by having no valves; it moves air back and forth (like the tides) through the same set of tubes; these tubes both conduct fresh air to the alveoli and collect alveolar gas from them. Little or no gas is exchanged in these tubes; they are "dead space." This dead space in the air pump is a disadvantage in one respect: it requires more ventilation and more pump work. It is an advantage in another: it permits more space in the lungs for diffusion of gases because it

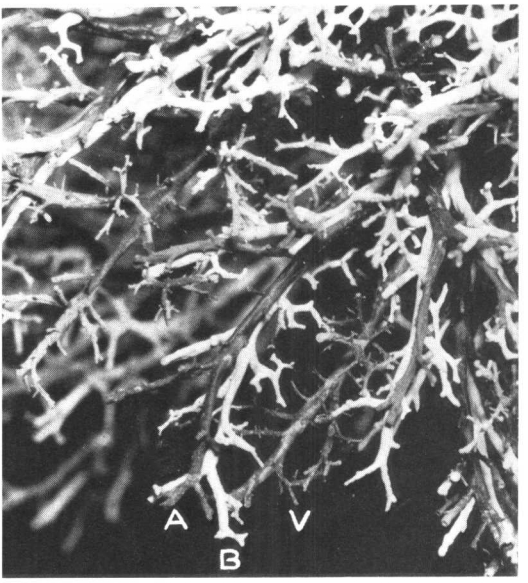

Fig. 1-6.—The blood and gas distributing and collecting systems. Arteries (*A*), bronchi (*B*), and veins (*V*) have been demonstrated by injecting them and digesting away all tissue. The artery and bronchus are close to each other. The vein is midway between the broncho-arterial rays. (Courtesy of Dr. Averill Liebow.)

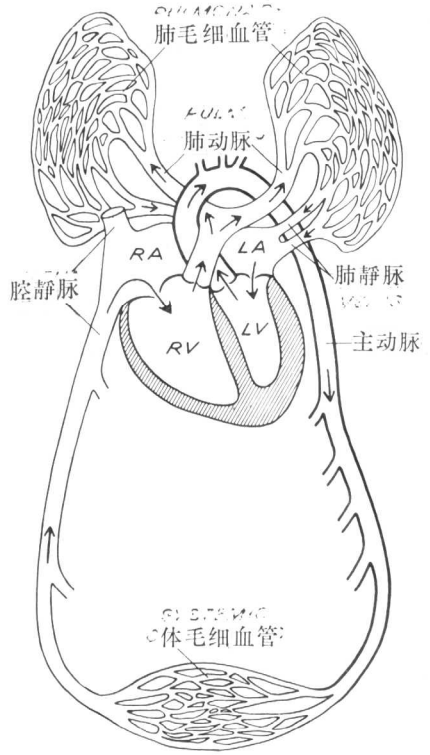

Fig. 1-5.—Schematic representation of the pulmonary and systemic circulations. *RA* = right atrium; *LA* = left atrium, *RV* = right ventricle; *LV* = left ventricle.

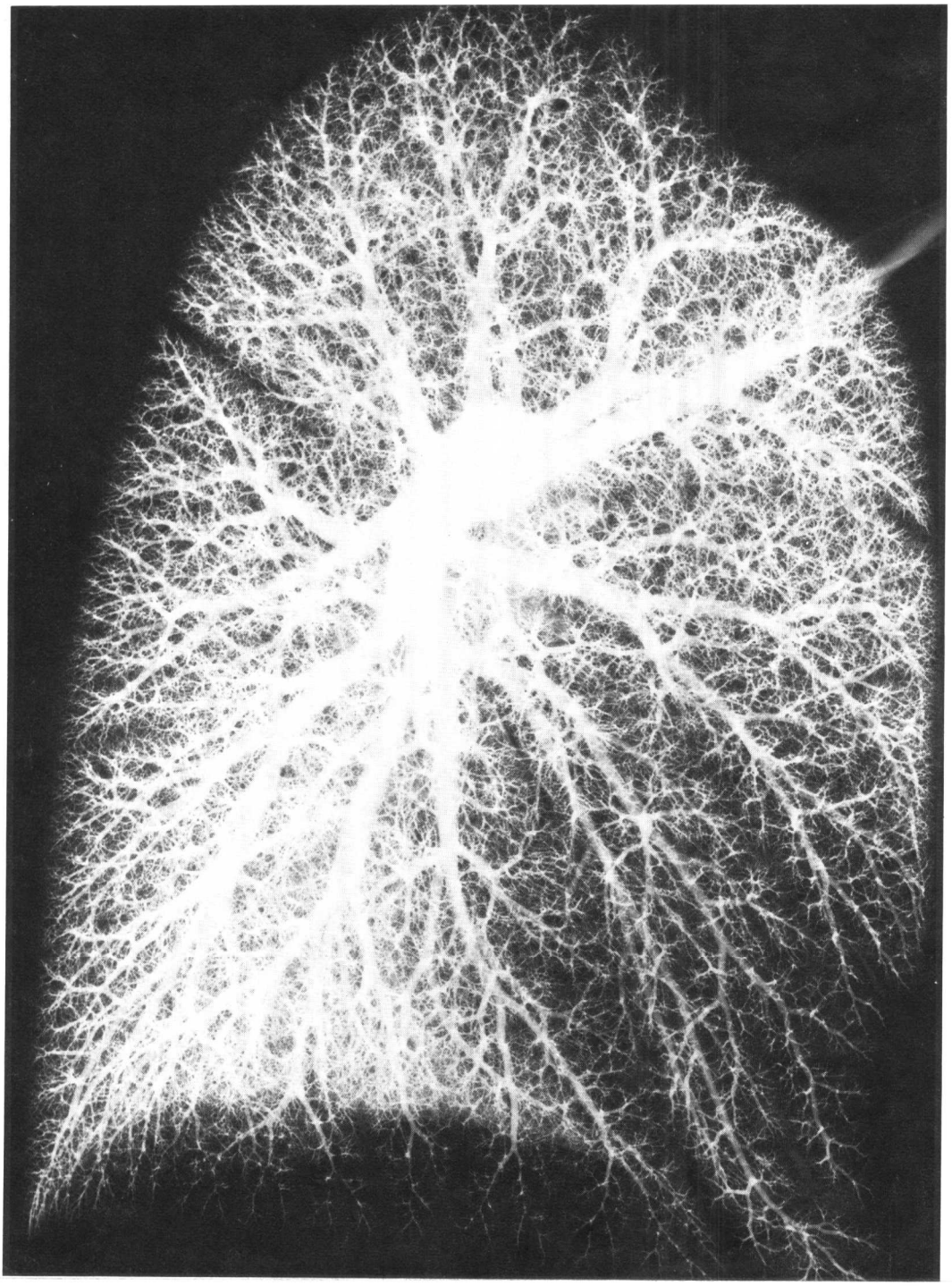

Fig. 1-7.—Angiogram of inflated human lung injected at autopsy with radiopaque material (Courtesy of Dr. Robert Wright; from Comroe, J. H.: Scient. Am. 214:56, 1966.)

eliminates the need for a different set of collecting tubes for expired gas. The air pump differs from the blood pump in another respect: it is a "negative" (subatmospheric), rather than a positive, pressure pump. A positive-pressure pump would *compress* the lungs, push alveolar gas out of the thorax and then allow fresh air to enter during recoil. The negative-pressure pump actively *enlarges* the thorax and lowers the pressure in the alveoli below atmospheric pressure so that air, at atmospheric pressure, flows in; it then recoils passively to its resting position to push air out.

To meet the varying needs of tissue cells, the heart and lungs must be variable pumps. Ideally, they should also be regulated with exquisite precision, so that they meet every need with the least cost in energy. Further, the supply of air and the supply of blood produced by the two pumps must be matched not only in overall amounts but also in every region of the lung. This requires responsive decision centers, supplied with necessary information and the power to enforce decisions.

Respiratory regulation, of course, involves more than maintaining a supply of air for gas exchange. For example, expired air is used for speaking, singing, blowing, coughing; respiratory muscles are involved in sighing, yawning, laughing, sobbing, hiccuping, sucking, sniffing, straining and vomiting. In some animals, expired air is an important means of eliminating heat. And there are special regulatory mechanisms to protect the lung from the entry of solids, liquids and irritant gases.

The pulmonary gas exchange system is not an end in itself. It exists to meet the needs of organs, tissues and cells. Physiologists usually think of respiration as the movement of the lungs, thorax and air. Biochemists think of respiration as the cellular processes in tissues that use O_2 and give off CO_2. Some call the first "external respiration" and the second "internal respiration" or "tissue respiration." In this volume we shall discuss all of the processes involving exchange of gases—between air and the alveoli, between the alveoli and pulmonary capillary blood, between tissue capillaries and tissue cells and between air-containing spaces and blood. We shall leave to the biochemists the actual cellular processes that use O_2.

2

Alveolar Ventilation

THE MOST IMPORTANT FUNCTION of the lung and of pulmonary ventilation is to supply tissue cells with enough O_2 and to remove excess CO_2. To accomplish this, pulmonary ventilation must increase the partial pressure of O_2 in the alveoli well above that in the venous blood flowing through the alveolar capillaries; this loads the blood destined for tissue cells with O_2. It must also lower the partial pressure of CO_2 in the alveoli below that in venous blood; this unloads excess CO_2 from the blood destined for tissue cells. Since gases move between alveoli and their capillary blood and between tissues and their capillary blood because of a difference in their partial pressures, it is well to define partial pressures of gases at this time.

PARTIAL PRESSURE OF OXYGEN (P_{O_2}) AND OF CARBON DIOXIDE (P_{CO_2})

Partial Pressure of a Gas in a Mixture of Gases

P stands for pressure; P_{O_2} is the pressure of oxygen and P_{CO_2} the pressure of carbon dioxide (Table 2-1). A pure gas does not behave like a continuous fluid, but like an enormous number of tiny particles. At atmospheric pressure, 1 mole of a gas contains 6×10^{23} particles (Avogadro's number), and these occupy 22.4 L at 0 C. These particles (molecules) are separated by distances that are large in relation to their own dimensions. They are in a continuous state of random motion, but exert no forces on one another except when they collide. During collision with other molecules or with the walls of the containing vessels, there is no chemical reaction; the collisions may be regarded as perfectly elastic, and the pressure depends on the number of collisions.

In 1643 Torricelli found that the total pressure of atmospheric gases at sea level was sufficient to maintain a column of mercury 760 mm high. For more than 300 years thereafter, the total and partial pressures of gases have been expressed in mm Hg. A few years ago, some respiratory physiologists decided to replace the clumsy term "millimeters of mercury" with "torr." "Torr" specifically refers to the pressure required to support a column of mercury 1 mm high when the mercury is of standard density and subject to standard acceleration. (These conditions are met at 0 C and 45 latitude, where the acceleration of gravity is 980.6 cm/sec^2.) "Torr" has become a synonym for "mm Hg." In this book I use "torr" to refer to partial or total pressures of gases. I have

TABLE 2-1.—PARTIAL PRESSURE OF GASES: SYMBOLS AND DEFINITIONS

P	= Pressure
P_{O_2} or P_{CO_2} or P_{N_2} or P_{H_2O}	= Partial pressure of oxygen or carbon dioxide or nitrogen or water
$P_{I_{O_2}}$	= Partial pressure of oxygen in inspired gas
$P_{A_{O_2}}$	= Partial pressure of oxygen in alveolar gas
$P_{a_{O_2}}$	= Partial pressure of oxygen in arterial blood
$P_{\bar{v}_{O_2}}$	= Partial pressure of oxygen in mixed venous blood

continued to use "mm Hg" for blood pressure because the term is still preferred by cardiovascular physiologists.

If we have a container of pure, dry O_2 at sea level, its P_{O_2} is the same as the total pressure, 760 torr, since all of the molecules are O_2. If instead we have a mixture of gases, the pressure exerted by each is the same as it would be if that gas alone occupied the whole volume (Dalton's law). For example, the gases in dry air are O_2(20.93%), CO_2(0.04%) and N_2 (79.03%). If the O_2 molecules were suddenly alone and the volume of the container remained the same, there would be only 20.93% as many collisions as before, and the pressure would be 20.93% of 760, or 159.1 torr. Likewise, if the CO_2 occupied the volume alone, the pressure would be 0.04% of 760, or 0.3 torr. Nitrogen in a similar situation would have a pressure of 79.03% of 760, or 600.6 torr. The sum of all the partial pressures, 159.1 + 0.3 + 600.6, gives the total pressure, 760 torr.

In the lungs, the gases are O_2, CO_2, N_2 and H_2O (as water vapor); at 37 C their partial pressures are 104, 40, 569 and 47, respectively (Table 2-2). These are average values for healthy resting man at sea level; values of P_{O_2}, P_{CO_2} and P_{N_2} fluctuate from breath to breath and during a single breath. The partial pressure of a gas in a mixture of gases can be measured in many ways. Both O_2 and CO_2 have long been measured by chemical absorption technics in the Haldane, Van Slyke or Scholander apparatus. Oxygen can now be measured by a rapid O_2 electrode or by a paramagnetic analyzer, CO_2 by a continuous infrared analyzer and N_2 by emission spectroscopy. These gases can also be measured by gas chromatography or mass spectrometry.

TABLE 2-2.—TOTAL AND PARTIAL PRESSURES OF GASES (TORR)*

	Dry Air	Moist Tracheal Air (37 C)	Alveolar Gas	Arterial Blood	Mixed Venous Blood
P_{O_2}	159.1†	149.2†	104†	100	40
P_{CO_2}	0.3	0.3	40	40	46
P_{H_2O}	0.0	47.0	47	47	47
P_{N_2}‡	600.6	563.5	569	573	573
P total	760.0	760.0	760	760	706¶

*Usual values in a resting, healthy man at sea level (barometric pressure = 760 torr).

†This is an approximate value and holds approximately only for man breathing air at sea level (760 torr). The total atmospheric pressure at Denver or Salt Lake City is about 640 torr, and the partial pressure of O_2 in inspired and alveolar gas is well below values for man at lea level.

‡Includes small amounts of rare gases.

¶See p. 276

Partial Pressure of Water Vapor

The partial pressure of water vapor in air is a special problem. The molecules of a liquid, like those of a gas, are in constant motion; those at the liquid-air surface tend to escape into the gas above the liquid. The greater the temperature, the greater is the kinetic energy of the water molecules and the greater their tendency to escape. Therefore, water-vapor pressure depends directly on temperature. Water vapor at body temperature (37 C) maintains a partial pressure of 47 torr, regardless of changes in barometric pressure. Some water-vapor pressures covering the range encountered in physiologic conditions are given in Table 2-3.

Room air usually contains some water vapor. But, regardless of whether it contains water vapor or not, it becomes saturated with water vapor at body temperature as soon as it is drawn through the nose, mouth and pharynx. Therefore, inspired gas in the trachea has a P_{H_2O} of 47 torr. Since the total gas pressure in the trachea must equal atmospheric pressure (760 torr), only 760 − 47, or 713, torr is available for the sum of the partial pressures of O_2, CO_2 and N_2.

TABLE 2-3.—WATER VAPOR PRESSURES (P_{H_2O}) AT DIFFERENT TEMPERATURES

Temp. (C)	P_{H_2O} (torr)	Temp. (C)	P_{H_2O} (torr)
20	17.5	29	30.0
21	18.7	30	31.8
22	19.8	31	33.7
23	21.1	32	35.7
24	22.4	33	37.7
25	23.8	34	39.9
26	25.2	35	42.2
27	26.7	36	44.6
28	28.3	37	47.0