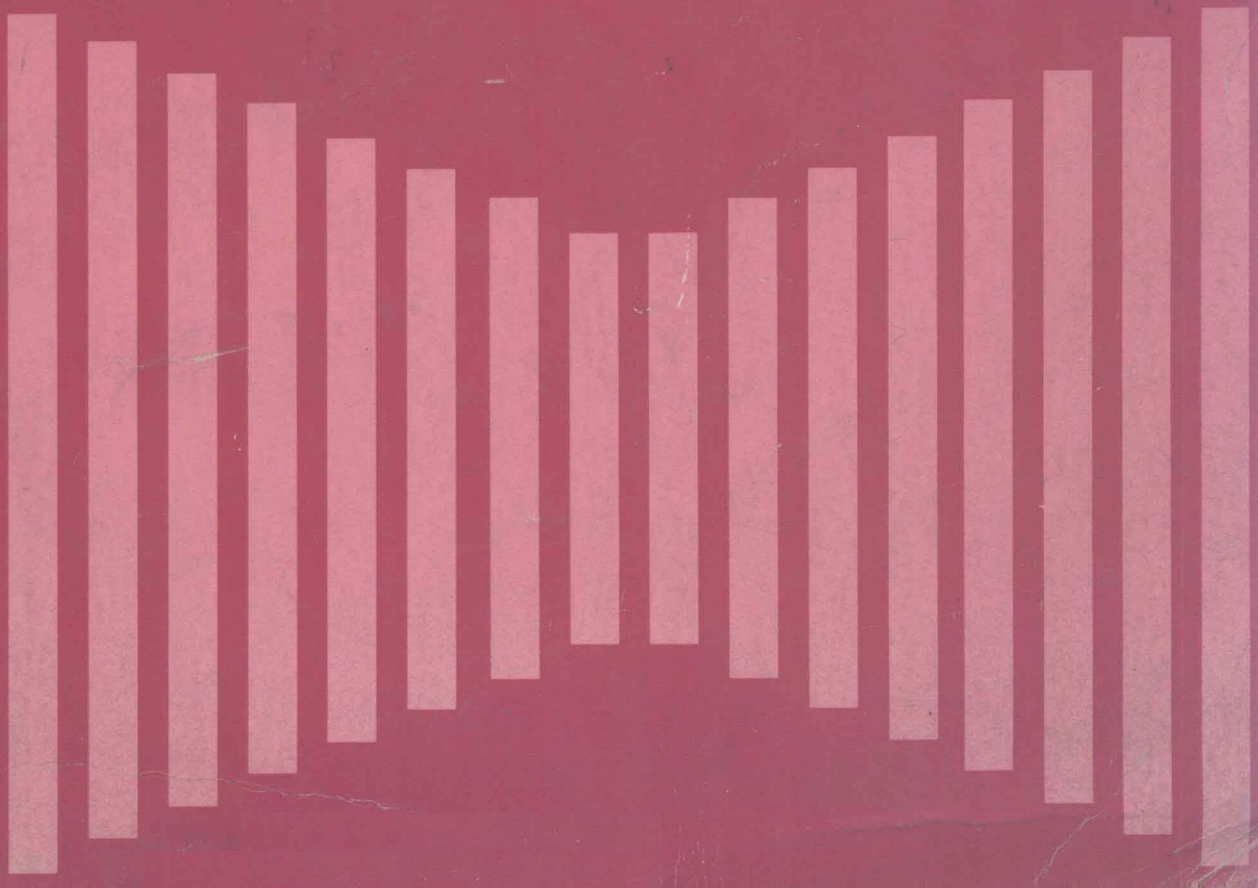
ttle, Brown
ew Book

REVIEW OF PATHOPHYSIOLOGY

Christian E. Kaufman, Jr., M.D.
Solomon Papper, M.D.



REVIEW OF PATHOPHYSIOLOGY

Edited by

Christian E. Kaufman, Jr., M.D.

Associate Professor of Medicine, University of Oklahoma College of Medicine; Staff Physician, Veterans Administration Medical Center, Oklahoma City

Solomon Papper, M.D.

Distinguished Professor and Head, Department of Medicine, University of Oklahoma College of Medicine; Staff Physician, Veterans Administration Medical Center, Oklahoma City

Little, Brown and Company Boston/Toronto

First Edition

Library of Congress Catalog Card No. 82-84376

ISBN 0-316-48339-7

Printed in the United States of America

HAL

Contributing Authors

Ralph C. Beckett, M.D.	Formerly Assistant Professor of Medicine, University of Oklahoma College of Medicine. Currently in private practice, Cedar Rapids, Iowa
Sylvia S. Bottomley, M.D.	Professor of Medicine, University of Oklahoma College of Medicine; Staff Physician, Veterans Administration Medical Center, Oklahoma City
Ronald D. Brown, M.D.	Professor of Medicine, University of Oklahoma College of Medicine; Staff Physician, Veterans Administration Medical Center, Oklahoma City
Jay P. Cannon, M.D.	Associate Professor of Surgery, University of Oklahoma College of Medicine; Staff Physician, Veterans Administration Medical Center, Oklahoma City
Philip C. Comp, M.D., Ph.D.	Associate Professor of Medicine, University of Oklahoma College of Medicine, Oklahoma City
Alfred F. Connors, M.D.	Assistant Professor of Medicine, Pulmonary Division, Case Western Reserve University School of Medicine; Director, Medical Intensive Care Unit, Cleveland Metropolitan General Hospital, Cleveland
Anthony W. Czerwinski, M.D.	Clinical Professor, Department of Medicine, University of Oklahoma College of Medicine, Oklahoma City
Ann L. DeHart, M.D.	Formerly Fellow, Pulmonary Disease Section, Department of Medicine, University of Oklahoma College of Medicine. Currently in private practice, Albuquerque, New Mexico
E. Randy Eichner, M.D.	Professor of Medicine and Chief, Hematology Section, Department of Medicine, University of Oklahoma College of Medicine; Staff Physician, Veterans Administration Medical Center, Oklahoma City
Robert B. Epstein, M.D.	Eason Professor and Chief, Oncology Section, Department of Medicine, University of Oklahoma College of Medicine; Staff Physician, Veterans Administration Medical Center; Director of Clinical Oncology, Oklahoma Memorial Research Foundation, Oklahoma City
Michael D. Ezekowitz, M.D., Ph.D.	Associate Professor, Departments of Medicine and Radiology, Yale University School of Medicine, New Haven, Connecticut
Arnold J. Felsenfeld, M.D.	Assistant Professor of Medicine, University of Oklahoma College of Medicine; Staff Physician, Veterans Administration Medical Center, Oklahoma City
Barry A. Gray, M.D., Ph.D.	Associate Professor of Medicine, University of Oklahoma College of Medicine; Director, Medical Intensive Care Unit, Veterans Administration Medical Center, Oklahoma City
C. G. Gunn, M.D.	Professor of Medicine, University of Oklahoma College of Medicine; Staff Physician, Veterans Administration Medical Center, Oklahoma City

John R. Higgins, M.D.	Associate Professor and Associate Chairman, Department of Medicine, and Chief, Endocrinology and Metabolism Section, Texas Tech University School of Medicine, Lubbock
Christian E. Kaufman, Jr., M.D.	Associate Professor of Medicine, University of Oklahoma College of Medicine; Staff Physician, Veterans Administration Medical Center, Oklahoma City
David C. Kem, M.D.	Professor of Medicine and Chief, Endocrinology, Metabolism, and Hypertension Section, Department of Medicine, University of Oklahoma College of Medicine; Staff Physician, Veterans Administration Medical Center, Oklahoma City
Henry F. Krous, M.D.	Associate Professor of Pathology and Pediatrics, University of Oklahoma College of Medicine, Oklahoma City
Ralph Lazzara, M.D.	Professor of Medicine and Chief, Cardiovascular Section, Department of Medicine, University of Oklahoma College of Medicine; Staff Physician, Veterans Administration Medical Center, Oklahoma City
David C. Levin, M.D.	Associate Professor of Medicine, University of Oklahoma College of Medicine; Staff Physician, Veterans Administration Medical Center, Oklahoma City
Francisco Llach, M.D.	Professor of Medicine and Chief, Nephrology Section, Department of Medicine, University of Oklahoma College of Medicine; Staff Physician, Veterans Administration Medical Center, Oklahoma City
D. Robert McCaffree, M.D.	Associate Professor of Medicine, University of Oklahoma College of Medicine; Medical Director, Intensive Care Unit, Oklahoma Memorial Hospital; Staff Physician, Veterans Administration Medical Center, Oklahoma City
James A. Merrill, M.D.	Professor of Gynecology and Obstetrics and Professor of Pathology, University of Oklahoma College of Medicine, Oklahoma City
John A. Mohr, M.D.	Professor of Medicine, University of Oklahoma College of Medicine; Assistant Chief, Medical Service, Veterans Administration Medical Center; Chief, Medical Service, O'Donoghue Rehabilitation Institute, Oklahoma City
Thomas L. Murphy, M.D.	Director, Respiratory Therapy Department, Gaston Memorial Hospital, Gastonia, North Carolina
Don P. Murray, M.D.	Assistant Professor, Department of Medicine, University of Oklahoma College of Medicine; Staff Physician, Veterans Administration Medical Center, Oklahoma City
J. Lee Murray, M.D.	Faculty Associate, Department of Clinical Immunology and Biological Therapy, M. D. Anderson Hospital and Tumor Institute, Houston, Texas
John W. Nelson, M.D.	Professor and Head, Department of Neurology, University of Oklahoma College of Medicine; Chief, Neurology Service, Veterans Administration Medical Center, Oklahoma City

Thasana Nivatpumin, M.D.	Associate Professor of Medicine, University of California at Los Angeles, School of Medicine; Director, Cardiac Catheterization Laboratory, Cedars-Sinai Medical Center, Los Angeles
Samuel R. Oleinick, M.D., Ph.D.	Professor of Medicine and Adjunct Professor of Microbiology-Immunology, University of Oklahoma College of Medicine; Staff Physician, Veterans Administration Medical Center, Oklahoma City
Solomon Papper, M.D.	Distinguished Professor and Head, Department of Medicine, University of Oklahoma College of Medicine; Staff Physician, Veterans Administration Medical Center, Oklahoma City
James A. Pederson, M.D.	Professor of Medicine, University of Oklahoma College of Medicine; Director, Renal Failure Care Unit, Veterans Administration Medical Center, Oklahoma City
Laura I. Rankin, M.D.	Assistant Professor of Medicine, University of Oklahoma College of Medicine; Staff Physician, Veterans Administration Medical Center, Oklahoma City
Robert A. Rankin, M.D.	Assistant Professor of Medicine, University of Oklahoma College of Medicine; Director, Endoscopy Service, Oklahoma Memorial Hospital and Veterans Administration Medical Center, Oklahoma City
Morris Reichlin, M.D.	Professor of Medicine and Chief, Immunology Section, Department of Medicine, University of Oklahoma College of Medicine; Staff Physician, Veterans Administration Medical Center; Head, Arthritis and Immunology Laboratory, Oklahoma Medical Research Foundation, Oklahoma City
Dwight W. Reynolds, M.D.	Assistant Professor of Medicine, University of Oklahoma College of Medicine; Staff Physician, Veterans Administration Medical Center, Oklahoma City
Everett R. Rhoades, M.D.	Formerly Professor of Medicine and Chief of Infectious Diseases Section, Department of Medicine, University of Oklahoma College of Medicine, Oklahoma City. Currently Assistant Surgeon General and Director, Indian Health Service, Washington, D.C.
Robert H. Roswell, M.D.	Assistant Professor of Medicine, University of Oklahoma College of Medicine; Staff Physician, Veterans Administration Medical Center, Oklahoma City
Sami I. Said, M.D.	Professor of Medicine and Chief, Pulmonary Disease and Critical Care Section, Department of Medicine, University of Oklahoma College of Medicine; Staff Physician, Veterans Administration Medical Center, Oklahoma City
Eliot Schechter, M.D.	Professor of Medicine, University of Oklahoma College of Medicine; Director, Cardiac Catheterization Laboratory, Veterans Administration Medical Center, Oklahoma City
Russell T. Schultz, M.D.	Professor of Medicine, University of Oklahoma College of Medicine; Chief of Rheumatology, Veterans Administration Medical Center, Oklahoma City
Robert B. Slease, M.D.	Associate Professor of Medicine, University of Oklahoma College of Medicine; Staff Physician, Veterans Administration Medical Center, Oklahoma City

Dilip L. Solanki, M.D.	Associate Professor of Medicine, University of Oklahoma College of Medicine; Staff Physician, Veterans Administration Medical Center, Oklahoma City
Udho Thadani, M.B.B.S., M.R.C.P.	Associate Professor of Medicine and Vice-Chief, Cardiovascular Section, University of Oklahoma College of Medicine; Staff Physician, Veterans Administration Medical Center, Oklahoma City
James H. Wells, M.D.	Associate Professor of Medicine, University of Oklahoma College of Medicine; Staff Physician, Veterans Administration Medical Center, Oklahoma City
Jack D. Welsh, M.D.	Professor of Medicine and Chief, Digestive Disease and Nutrition Section, Department of Medicine, University of Oklahoma College of Medicine; Staff Physician, Veterans Administration Medical Center, Oklahoma City
Robert Whang, M.D.	Professor and Vice-Head, Department of Medicine, University of Oklahoma College of Medicine; Chief, Medical Service, Veterans Administration Medical Center, Oklahoma City
Michael F. Wilson, M.D.	Professor of Medicine and Associate Professor of Radiology, University of Oklahoma College of Medicine; Associate Chief of Staff for Research, Veterans Administration Medical Center, Oklahoma City

Preface

Knowledge of the mechanisms of disease is vast and rapidly expanding. The purpose of *Review of Pathophysiology* is to summarize selected information that is clinically relevant or likely to become so in the near future; it is not intended as a comprehensive text for this important field.

The term *pathophysiology* refers to the study of alterations in normal body function (physiology and biochemistry) that result from disease processes. Since a knowledge of physiology is essential to an understanding of pathophysiology, each chapter begins with a brief description of normal function, followed by a succinct review of common or classic disease processes. Our goal is to provide understanding of why and how disordered function occurs. Each chapter is concluded by one or two case studies (clinical examples) and related discussions to reinforce important principles and provide clinical relevance.

Review of Pathophysiology was designed to furnish the second-year medical student with a base of clinical information on which to build during subsequent years. In trying to bridge the gap between the basic sciences and bedside observation, we hope we have created a useful format for students, house staff, and practicing clinicians seeking a discussion of pathophysiology that is less detailed than that available in the standard texts.

We wish to thank each of the contributing authors for sharing knowledge and expertise. We are grateful to Beverly Clarke and Libby Price for editorial assistance and to Susie Rose for secretarial support.

C. E. K.
S. P.

Contents

Contributing Authors vii
Preface xi

John A. Mohr	I	**Aging**
	1	Physical Consequences of Aging 3
Michael D. Ezekowitz	II	**Cardiovascular Disease**
Ralph Lazzara	2	Electrophysiologic Basis of Cardiac Arrhythmias 11
Thasana Nivatpumin	3	Myocardial Contraction and Cardiac Performance 21
Dwight W. Reynolds	4	Common Forms of Volume and Pressure Overload 27
Eliot Schechter	5	Atherosclerosis 33
Udho Thadani	6	Biochemical, Physiologic, and Pathologic Consequences of Ischemia 39
Michael F. Wilson	7	Clinical Manifestations of Coronary Artery Disease 45
	8	Valvular Heart Disease 50
	9	Intracardiac Shunts 58
	10	Congestive Heart Failure 65
	11	Mechanisms of Shock 73
Ronald D. Brown	III	**Endocrinology, Metabolism, and Hypertension**
John R. Higgins	12	Hormone Action 81
David C. Kem	13	Anterior and Posterior Pituitary 85
Robert H. Roswell	14	Adrenal-ACTH 90
	15	Thyroid and TSH 96
	16	Hypertension 101
	17	Diabetes Mellitus and Glucose Metabolism 106
	18	Reproductive Endocrinology 111
Robert A. Rankin	IV	**Gastroenterology**
Jack D. Welsh	19	The Esophagus 119
	20	Peptic Ulcer Diseases of the Stomach and Duodenum 125
	21	The Pancreas 131
	22	The Gallbladder and Biliary Tract 137
	23	The Liver 141
	24	Maldigestion, Malabsorption, and Diarrhea 149
	25	Gastrointestinal Malignancies 154
Sylvia S. Bottomley	V	**Hematology**
Philip C. Comp	26	Introduction to Hematology 159
Dilip L. Solanki	27	Disorders of the Erythron 160
	28	Neutrophil Disorders 169
	29	Platelets 175
	30	Disorders of Blood Coagulation 181
Samuel R. Oleinick	VI	**Immunology and Rheumatology**
Morris Reichlin	31	Immediate Hypersensitivity Disease 189
Russell T. Schultz	32	Allergic Respiratory Diseases 194
James H. Wells	33	Immunologically Mediated Disease 200
	34	Inflammatory Rheumatic Diseases (Noninfectious): Mediation by Immunologic Mechanisms 206
	35	Degenerative Joint Diseases and Gout 213
	36	Immunodeficiency 220

Everett R. Rhoades	***VII***	***Infection***
	37	Inflammation 231
	38	Hyperthermia and Fever 238
Anthony W. Czerwinski	**VIII**	**Nephrology**
Arnold J. Felsenfeld	39	Disorders of Sodium and Water Metabolism 247
Christian E. Kaufman, Jr.	40	Potassium Homeostasis 260
Henry F. Krous	41	Hydrogen Ion Homeostasis: Metabolic Acidosis and Alkalosis 268
Francisco Llach	42	Calcium, Phosphate, and Vitamin D 279
James A. Pederson	43	Glomerulonephritis and the Acute Nephritic Syndrome 287
Laura I. Rankin	44	The Nephrotic Syndrome 298
	45	Acute Renal Failure 303
	46	The Uremic State 308
	47	Metabolic Bone Disease 313
	48	Renal Cell Carcinoma: Mechanisms of Clinical Manifestations 322
C. G. Gunn	**IX**	**Neurology and Pain**
John W. Nelson	49	Pain 327
	50	Epilepsy 333
	51	Cerebrovascular Disease 337
	52	The Upper Motor Neuron System and the Motor Unit 340
Don P. Murray	**X**	**Nutrition**
Robert Whang	53	Clinical Malnutrition 347
E. Randy Eichner	**XI**	**Oncology**
Robert B. Epstein	54	Carcinogenesis, Cell Kinetics, and Tumor Immunology 355
J. Lee Murray	55	Extraneoplastic Manifestations of Malignancies 367
Robert B. Slease	56	Neoplasms of the Immune System 375
	57	Cancer of the Breast 386
Ralph C. Beckett	**XII**	**Pulmonary Disease**
Alfred F. Connors	58	Pulmonary Gas Exchange 395
Ann L. DeHart	59	Pulmonary Mechanics 405
Barry A. Gray	60	Control of Breathing 413
David C. Levin	61	Reversible Obstructive Airways Disease (Asthma) 421
D. Robert McCaffree	62	Chronic Airflow Limitation 430
Thomas L. Murphy	63	Interstitial Lung Disease 434
Sami I. Said	64	Pulmonary Edema 442
	65	Pulmonary Vascular Disease 449
	66	Pulmonary Neoplastic Disease 455
Jay P. Cannon	**XIII**	**Surgery and Trauma**
	67	The Metabolic Response to Surgery, Injury, and Trauma 463
James A. Merrill	**XIV**	**Toxemias of Pregnancy**
	68	Hypertensive Disorders (Toxemia) of Pregnancy 475
		Questions, Answers, and Analyses 485
		Index 525

I Aging

John A. Mohr

Notice. The indications and dosages of all drugs in this book have been recommended in the medical literature and conform to the practices of the general medical community. The medications described do not necessarily have specific approval by the Food and Drug Administration for use in the diseases and dosages for which they are recommended. The package insert for each drug should be consulted for use and dosage as approved by the FDA. Because standards for usage change, it is advisable to keep abreast of revised recommendations, particularly those concerning new drugs.

1 Physical Consequences of Aging

I. Introduction. There are many physical changes that occur in people directly associated with, or as a result of, the aging process. Failure to recognize this may lead to unnecessary, expensive, and troublesome diagnostic procedures. Furthermore, older people respond differently than younger ones (often adversely) to disease and to our therapeutic endeavors. These differences must be recognized in order to ensure an optimal outcome.

II. Changes in stature and posture

A. Shrinkage in height is common in the elderly. The long bones do not undergo significant shortening; hence, the loss of stature can be ascribed to shortening of the spinal column as a result of both narrowing of the disks and loss in height of the individual vertebrae. In the middle years, this is due primarily to thinning of the disks, whereas in later years vertebral collapse is the major reason for loss of height. Narrowing osteoporotic vertebrae are almost universal in elderly females, but occur less frequently in males. Thus, the elderly are, in general, characterized by shortened trunks and comparatively long extremities.

B. Other changes caused by bone shortening. The thinning of the intervertebral disk and centrum also affects the neck, and to compensate for the upper thoracic spine kyphosis, the head may be tilted backward. In association with shortening of the neck, the thyroid may descend, making it difficult to palpate the lower poles of the thyroid. With shortening of the spine and lengthening of the aorta, the aortic arch elevates and may bring the right innominate artery into the neck with possible kinking of the artery, thus producing a pulsating and sometimes visible mass behind the clavicular portion of the right sternocleidomastoid muscle. The enlarged, rigid aorta may compress the left innominate vein, resulting in dilatation of the left external jugular vein. This can best be seen with the patient sitting up at a 45-degree angle.

Shoulder width and chest size decrease with age. In elderly women, chest diameter decreases 3.3 cm and in elderly men it decreases 2.3 cm. When narrowing is marked, the apical impulse may be present in the anterior axillary line without significant cardiomegaly. Furthermore, the cervical and thoracic spine may become quite rigid, rendering invalid the usual maneuvers attempted in diagnosing meningitis or subarachnoid bleeding.

III. Body hair. Many elderly people demonstrate hair loss over the body suggestive of *alopecia totalis*. Racial, genetic, and sex-linked factors, as well as the changes that occur with aging, determine the amount of hair an individual possesses. American Indian males have little body and facial hair. Caucasian males tend to have far heavier beards, and the onset of graying is earlier than in other races. Facial hirsutism is extremely rare in Japanese women up to 88 years of age, whereas in aging Caucasian women it is quite common. In general, aging is associated with decreased hair everywhere except the face.

IV. Skin. Skin studies of people over the age of 64 have demonstrated lax skin in 94 percent and seborrheic keratoses and cherry angiomas in 88 percent and 75 percent, respectively. Over 75 percent had dry, scaly skin. Other

frequent skin features in the elderly include senile purpura, warts, and papillomas. The purpura appear to be a result of the loss of subcutaneous tissue supporting the skin capillaries; hence, minor trauma readily results in ecchymotic lesions. These "spontaneous bruises" occur most frequently on the forearms. There is no evidence that vitamin C deficiency plays any role in their etiology. The number of cells present in the skin declines progressively with age. By the fifth decade of life, the total cell count has decreased almost 50 percent.

V. Eyes

A. Arcus senilis. One of the most common ocular signs of aging is arcus senilis, i.e., a yellowish-white opaque ring around the iris. It does not interfere with vision and is not related to serum cholesterol; it is a result of deposition of fatty substances in Bowman's and Descemet's membranes.

B. Visual changes. Although presbyopia (diminished ability of the lens to focus at different distances) is the most common visual change that occurs in aging, cataracts, macular degeneration, and glaucoma are more serious.

1. Cataracts. Cataracts result from opacification of the lens. The lens, a protein-rich organ, doubles its weight and volume in a lifetime. The lens is enclosed by a capsule, layers of which degenerate and form a hard nucleus inside as it grows with age. At the same time, the capsule loses elasticity and accommodation becomes more difficult, thereby contributing to presbyopia.

2. Macular degeneration. Macular degeneration results from ischemic changes in the retina, and its frequency increases with advancing age. Impaired vascular supply, especially to the periphery, leads to hyaline infiltration, calcification, and fatty degeneration. Similar changes in the fovea result in impairment of visual acuity.

3. Glaucoma. As the lens size increases, the anterior chamber size decreases, producing a more acute angle between the root of the iris and the posterior corneoscleral surface. This, then, clogs the trabecular system, resulting in an increased pressure in the eye (glaucoma).

VI. Ears. The age-related changes in the ears are similar to those in the eyes: a slow, progressive loss of acuity known as presbycusis. There is evidence that the noise levels of modern living predispose to lower the age at which hearing begins to deteriorate.

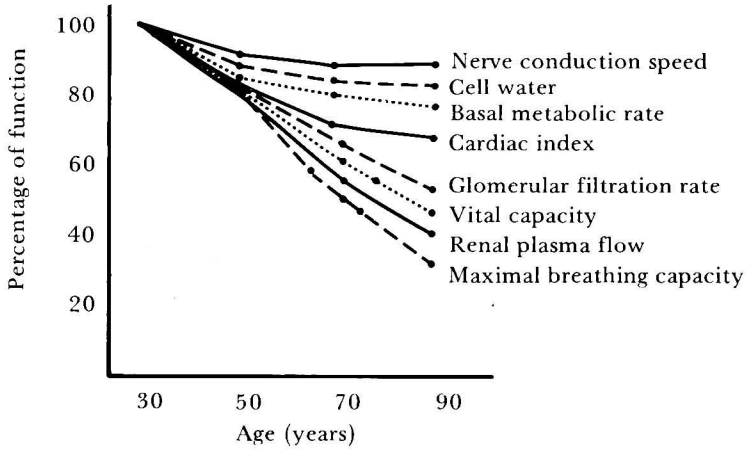
The auditory system consists of four major parts: (1) the middle ear (sound conduction); (2) the inner ear (analysis of mechanical frequency and stimulus transformation); (3) the peripheral neuron (conduction and acoustic selectivity); and (4) the central auditory pathway (integration and interpretation). The latter three are affected by age. The sensory cells of the cochlea appear to be affected first; as a result, high-frequency tones are lost. Impairment of the inner ear results in disturbed intelligibility of speech. With a steady loss of ganglion cells in the auditory nerve, the elderly person loses the ability to discriminate or select individual conversations.

VII. Body mass

A. Muscles. Muscles are composed of nonmitotic cells and achieve their optimum size and strength when an individual reaches maturity in the middle 20s. Athletic individuals and manual workers who stay in training maintain their muscle mass and strength well into the sixth decade, but then there is a steady atrophy. In general, lean body mass (mus-

Figure 1-1

Influence of age on organ systems. (Modified from graph and text of F. Bourliere, Aging in the individual. Report of the Canadian Conference on Aging, *Toronto, 1966, pp. 23–36. In R. Cape,* Aging: Its Complex Management. *New York: Harper & Row, 1978, pp. 13–38. By permission of Harper & Row.)*



cles, liver, brain, and kidneys) decreases 20 to 50 percent by the age of 70 or 80. A decrease in intracellular water occurs, reflecting changes in cell mass, but there is no associated change in extracellular volume. The clinical implications are real: (1) the need for energy-providing food is reduced; and (2) the target organ mass on which drugs act is reduced. It follows that less food and smaller doses of drugs are required in old people.

B. Other organ systems. Most organ systems are similarly affected by age (Fig. 1-1). Particularly prominent changes are described under subsequent headings.

VIII. Nervous system

A. Nerve cell loss. Nerve cells are postmiotic and, when they are lost, are not replaced. In some cortical areas the loss of cells may be 45 percent. Cerebellar loss may be as high as 25 percent. Even when cells are not lost, they may undergo changes that alter function. For instance, the pyramidal cells in the third layer of the cerebral cortex show a progressive decrease in the number of interconnections between dendrites, thus implying loss of function.

B. Cellular changes. At the cellular level the most widely studied change is the intracellular accumulation of lipofuscin pigment, which is highly proportionate to age. Despite the previously mentioned changes, intellectual function is usually well maintained. There are, however, several anatomic changes that do correlate with dementia. These are senile plaques, neurofibrillary tangles, and granulovascular degeneration. Whether senile dementia is a manifestation of aging or a disease process remains unknown.

C. Brain blood flow. Recent studies show that from ages 17 to 80 cerebral blood flow declines from 79 to 46 ml per minute per 100 g of brain tissue. A decline in cerebral oxygen consumption from 3.6 to 2.7 ml per minute per 100 g of brain may be the primary reason for the decreased blood flow.

D. Nerve conduction. Nerve conduction velocity is most rapid in myelinated fibers and to some degree is proportional to the diameter of the neuron. Motor conduction velocities of the ulnar nerve in infants is about 30 meters per second, and by the age of 5 years reaches max-

imum adult values (slightly less than 60 m/sec). After the fifth decade of life, the velocity progressively decreases to about 50 meters per second by the eighth or ninth decade.

IX. Cardiovascular system

A. Heart

1. **Myocardium.** In humans the left ventricular wall is usually 25 percent thicker at age 80 than at age 30. There is an increased collagen content and fibrosis in the aged heart; however, their effects on cardiodynamics are unknown.
2. **Heart rate.** The resting heart rate in humans is unchanged by age. When related to body mass, the resting stroke volume and cardiac output are unchanged. However, during maximal work, both stroke volume and cardiac rate are decreased; thus, cardiac output is reduced. Between the third and the eighth decades, the decrease amounts to slightly less than 1 percent per year. The time required for the heart rate to return to normal after exercise is also prolonged with age.
3. **Oxygen consumption.** Maximal oxygen consumption declines at about the same rate as does cardiac output. Obesity, inactivity, and smoking hasten this decline to some extent. At equal work levels, the oxygen uptake is identical in the young and old; thus, the difference lies in work capacity, not in efficiency of oxygen extraction.
4. **Electrocardiographic changes.** The electrocardiogram pattern shows little change with age. However, small but significant increases in the P–R, QRS, and Q–T intervals are frequent.

B. Blood vessels. Elastin, which gives arteries their resilience, diminishes with age. These fibers progressively straighten, fray, split, and fragment. This process involves both the media of the elastic arteries and the elastic lamina of the muscular arteries. The vascular distensibility is even further compromised by the increasing amount of collagen in the vessels and the cross-linkage of collagen fibers into bundles of larger size. The decrease in distensibility of vessels is reflected in an increase in the pulse wave velocity of blood vessels. The aortic pulse wave velocity increases from 4.1 meters per second at age 5 to 10.5 meters per second at age 65. The change in pulse wave velocity is independent of atherosclerosis. It has been estimated that the energy lost in pulsatile work doubles in the aged because of this diminished elasticity.

X. Renal function. At birth, the human kidney contains approximately one million nephrons which increase in size until maturity. After maturity, there is a progressive loss of nephrons, owing to sclerosis or scarring of the glomeruli, followed by atrophy of the tubules. Between the ages of 25 and 85, the total nephron loss is 30 to 40 percent. The glomerular filtration rate decreases as much as 46 percent between the ages of 20 and 90. At the same time, renal plasma flow decreases by 53 percent. The reduction of renal tubular cell mass is reflected by a reduction of maximal tubular function; i.e., reabsorption of glucose, secretion of Diodrast, and para-aminohippuric acid are all decreased by about 45 percent. The ability to concentrate urine also decreases with age. Because of the age-related reduction in renal function, the dosage of those drugs dependent upon renal excretion should be modified. Since the aged patient has a reduced muscle mass, less creatinine is produced, and the serum creatinine does not rise in proportion to the fall in renal function. Hence, creatinine clearance, rather than serum creatinine, should be the criterion for renal function or dosage adjustment in the elderly.

XI. Pulmonary function

A. Lung mechanics. Even though the total lung capacity remains unchanged, residual volume and functional residual capacity increase with age, resulting in a decreased vital capacity. Indexes of flow, including maximum voluntary ventilation (MVV), maximum expiratory flow rate (MEFR), and 1-second forced expiratory volume (FEV_1), are all reduced, although airway resistance is unchanged.

B. Gas exchange. The aging process is also associated with impairment of gas exchange, as illustrated by reduced diffusing capacity for carbon monoxide, lowered arterial oxygen tension, and an increased alveolar-arterial oxygen gradient. These changes in lung mechanics and gas exchange are probably caused by a decline in elastic tissues of the lung, weakening of the respiratory muscles, and stiffness of the thoracic cage.

XII. The immune system

A. The thymus gland. The mass of the thymus gland begins to decrease after sexual maturity; by age 50 it has decreased in size to 15 percent of its maximum. The aged thymus is not merely small but is functionally deficient. In young, thymectomized animals given thymus transplants from donors of different ages, the animals receiving the youngest thymus had the T-lymphocyte population and T-cell function effectively restored, whereas those receiving thymuses from older animals did not. Levels of the thymic hormones, thymopoietin and thymosin, decline with age so that by the age of 60, both are undetectable in human serum.

B. T lymphocytes. Sheep red-blood-cell rosette formation is a test for the presence of mature human T lymphocytes. The number of rosette-forming thymocytes declines steadily with age. About 85 percent of the thymic lymphocytes from 20-year-olds form rosettes, while only 50 percent of the lymphocytes of 80-year-old patients do so. This suggests a marked decline in the ability of the thymus to stimulate T-cell maturation.

C. Hypersensitivity. Delayed hypersensitivity, a phenomenon mediated by the helper T cell, is depressed with age. For instance, tuberculin skin reactivity declines after the age of 70, at which time reactivation of tuberculosis is most common. The reaction of T lymphocytes to pokeweed mitogen and phytohemagglutinin is also depressed with age.

D. Antibody response. Antibody response depends upon a complex interaction of different lymphocyte classes and subclasses as well as antigen processing and presentation by macrophages. This interaction has been explored with respect to B and T cells by using an assay system in which plaques of sheep erythrocyte lysis provide a measurable endpoint. When killed staphylococci are used as the antigenic stimulus for isolated human lymphocytes, the number of plaque-forming cells (antibody response) declines with age. Other evidence of decreased humoral immunity includes a decreased antibody response to *Salmonella flagellin* and lower titers of antibodies to AB blood group antigens in older people.

E. Polymorphonuclear leukocytes. The functional properties of the polymorphonuclear leukocytes that can be quantified include migration, chemotaxis, adherence (to nylon fibers), phagocytosis, nitroblue tetrazolium (NBT) dye reduction, and *Candida*-killing activity. Studies in the elderly reveal: