
Braunwald: Heart Disease: A Textbook of Cardiovascular Medicine, 6th ed., Copyright © 200



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Heart Disease

A TEXTBOOK OF CARDIOVASCULAR MEDICINE

6th EDITION

Edited by

EUGENE BRAUNWALD M.D., M.D. (hon), Sc.D. (hon), F.R.C.P.

Vice President for Academic Programs, Partners HealthCare System
Distinguished Hersey Professor of Medicine
Faculty Dean for Academic Programs at Brigham and Women's Hospital and
Massachusetts General Hospital
Harvard Medical School
Boston, Massachusetts

DOUGLAS P. ZIPES M.D.

Distinguished Professor of Medicine, Pharmacology, and Toxicology
Director, Krannert Institute of Cardiology
Director, Division of Cardiology
Indiana University School of Medicine
Attending Physician
University Hospital, Wishard Memorial Hospital, and Roudebush Veterans
Affairs Hospital
Indianapolis, Indiana

PETER LIBBY M.D.

Mallinckrodt Professor of Medicine
Harvard Medical School
Chief, Cardiovascular Medicine
Brigham and Women's Hospital
Boston, Massachusetts

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To:
Elaine, Karen, Allison, and Jill
Joan, Debra, Jeffrey, and David
Beryl, Oliver, and Brigitte

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Contributors

DAVID H. ADAMS M.D.

Associate Professor of Surgery, Harvard Medical School; Associate Chief, Division of Cardiac Surgery
Medical Management of the Patient Undergoing Cardiac Surgery

JOSHUA ADLER M.D.

Assistant Clinical Professor of Medicine, University of California, San Francisco; Director, Ambulatory
Center, San Francisco, California
General Anesthesia and Noncardiac Surgery in Patients with Heart Disease

NADIR M. ALI M.D.

Assistant Professor of Medicine, Baylor College of Medicine, Houston; Interventional Cardiologist, (C)
Hemostasis, Thrombosis, Fibrinolysis, and Cardiovascular Disease

ELLIOTT M. ANTMAN M.D.

Associate Professor of Medicine, Harvard Medical School; Director, Samuel A. Levine Cardiac Unit,
Massachusetts
Acute Myocardial Infarction; Medical Management of the Patient Undergoing Cardiac Surgery

WILLIAM F. ARMSTRONG M.D.

Professor of Internal Medicine and Director, Echocardiography Laboratory, University of Michigan H
Associate Chair for Network Development, Department of Internal Medicine, University of Michigan H
Echocardiography

ARTHUR J. BARSKY M.D.

KENNETH R. BRIDGES M.D.

Associate Professor of Medicine, Harvard Medical School; Director, Joint Center for Sickle Cell and
Massachusetts
Hematological-Oncological Disorders and Cardiovascular Disease

MICHAEL R. BRISTOW M.D., Ph.D.

Professor of Medicine and Head, Division of Cardiology, University of Colorado Health Sciences C
Treatment of Heart Failure: Pharmacological Methods;
Management of Heart Failure

HUGH CALKINS M.D.

Professor of Medicine, Johns Hopkins University; Director of the Arrhythmia Service and Clinical EL
Maryland
Hypotension and Syncope

CHRISTOPHER P. CANNON M.D.

Assistant Professor of Medicine, Harvard Medical School; Cardiovascular Division, Department of M
Unstable Angina

AGUSTIN CASTELLANOS M.D.

Professor of Medicine, University of Miami School of Medicine; Director, Clinical Electrophysiology,
Medical Center, Miami, Florida
Cardiac Arrest and Sudden Cardiac Death

BERNARD R. CHAITMAN M.D.

Professor of Medicine, Cardiology Division, St. Louis University School of Medicine; Chief of Cardiac
Exercise Stress Testing

MELVIN D. CHEITLIN M.D., M.A.C.C.

Emeritus Professor of Medicine, University of California, San Francisco; Former Chief of Cardiology
Cardiovascular Disease in the Elderly

STEVEN D. COLAN M.D.

Associate Professor of Pediatrics, Harvard Medical School; Chief, Division of Noninvasive Cardiol
Massachusetts
Acquired Heart Disease in Children

WILSON S. COLUCCI M.D.

Professor of Medicine and Physiology, Boston University School of Medicine; Chief, Cardiovascular
Massachusetts
Pathophysiology of Heart Failure; Clinical Aspects of Heart Failure; Primary Tumors of the Heart

MARK A. CREAGER M.D.

Associate Professor of Medicine, Harvard Medical School; Director, Vascular Center, Brigham and

Houston, Texas
Lipid-Lowering Trials

HARVEY FEIGENBAUM M.D.

Distinguished Professor of Medicine and Director, Echocardiography Laboratories, Indiana University
Indianapolis, Indiana
Echocardiography

STACY D. FISHER M.D.

Instructor in Medicine/Cardiology, University of Rochester School of Medicine and Dentistry; Attending Physician
University of Rochester Medical Center and Children's Hospital at Strong, Rochester, New York
Cardiovascular Abnormalities in HIV-Infected Individuals

GERALD F. FLETCHER M.D.

Professor of Medicine, Mayo Medical School; Cardiovascular Disease, Prevention and Rehabilitation
Comprehensive Rehabilitation of Patients with Coronary Artery Disease

WILLIAM F. FRIEDMAN M.D.

J. H. Nicholson Professor of Pediatrics (Cardiology) and Senior Dean for Academic Affairs, University of California
Los Angeles, California
Congenital Heart Disease in Infancy and Childhood

PETER GANZ M.D.

Associate Professor of Medicine, Harvard Medical School; Director of Cardiovascular Research, Children's Hospital
Boston, Massachusetts
Coronary Blood Flow and Myocardial Ischemia

WILLIAM GANZ M.D.

Professor of Medicine, University of California, Los Angeles (UCLA), School of Medicine; Senior Research Scientist
Los Angeles, California
Coronary Blood Flow and Myocardial Ischemia

J. MICHAEL GAZIANO M.D., M.P.H.

Assistant Professor of Medicine, Harvard Medical School; Co-Director, Cardiovascular Epidemiology and Prevention
Center, Massachusetts Veterans' Epidemiology and Research Center, Boston VA Healthcare System
*Global Burden of Cardiovascular Disease;
Primary and Secondary Prevention of Coronary Heart Disease*

JACQUES GENEST M.D.

Associate Professor of Medicine, McGill University; Director, Division of Cardiology, McGill University
Risk Factors for Atherosclerotic Disease

BERNARD J. GERSH M.D., M.B., Ch.B., D.Phil.

Professor of Medicine, Mayo Medical Center; Consultant in Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota
Chronic Ischemic Heart Disease

Cardiac Pacemakers and Cardioverter-Defibrillators

CHARLES B. HIGGINS M.D.

Professor of Radiology, University of California, San Francisco, California
Newer Cardiac Imaging Modalities: Magnetic Resonance Imaging and Computed Tomography

MARK A. HLATKY M.D.

Professor of Health Research and Policy and of Medicine (Cardiovascular Medicine), and Chair, Division of Medicine, Stanford, California
Economics and Cardiovascular Disease

GARY S. HOFFMAN M.D.

Harold C. Schott Chair for Rheumatic and Immunologic Diseases and Professor of Medicine, Cleveland Clinic, Cleveland, Ohio
Immunologic Diseases, and Director, Center for Vasculitis Care and Research, Cleveland Clinic, Cleveland, Ohio
Rheumatic Diseases and the Cardiovascular System

ERIC M. ISSELBACHER M.D.

Instructor in Medicine, Harvard Medical School; Medical Director, Thoracic Aortic Center, Massachusetts General Hospital, Boston
Diseases of the Aorta

NORMAN M. KAPLAN M.D.

Clinical Professor of Medicine, University of Texas Southwestern Medical Center, Dallas, Texas
Systemic Hypertension: Mechanisms and Diagnosis;
Systemic Hypertension: Therapy

ADOLF W. KARCHMER M.D.

Professor of Medicine, Harvard Medical School; Chief, Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Boston
Infective Endocarditis

RALPH A. KELLY M.D.

Associate Professor of Medicine, Harvard University; Associate Physician, Division of Cardiology, Brigham and Women's Hospital, Boston
Treatment of Heart Failure: Pharmacological Methods

RICHARD E. KUNTZ M.D.

Associate Professor of Medicine, Harvard Medical School; Brigham and Women's Hospital, Boston
Percutaneous Coronary and Valvular Intervention

THOMAS H. LEE M.D., S.M.

Associate Professor of Medicine, Harvard Medical School; Medical Director, Partners Community Health Center, Boston
Guidelines: Electrocardiography;
Guidelines: Use of Exercise Tolerance Testing;
Guidelines: Use of Echocardiography;
Guidelines: Management of Heart Failure;
Guidelines: Cardiac Radionuclide Imaging;
Guidelines: Ambulatory Monitoring and Electrophysiological Testing;
Guidelines: Management of Cardiac Rhythm Disorders and Atrial Fibrillation; Guidelines

Cardiovascular Abnormalities in HIV-Infected Individuals

WILLIAM C. LITTLE M.D.

Chief of Cardiology and Professor of Medicine, Wake Forest University School of Medicine, Bowman
Carolina Baptist Hospital, Winston-Salem, North Carolina
Assessment of Normal and Abnormal Cardiac Function

BRIAN F. MANDELL M.D., Ph.D.

Clinical Professor of Medicine, Penn State University School of Medicine, Hershey, Pennsylvania; /
Medicine, Columbus, Ohio; Education Program Director, Rheumatic and Immunologic Diseases, C
Rheumatic Diseases and the Cardiovascular System

JOANN E. MANSON M.D., Dr.P.H.

Professor of Medicine, Harvard Medical School; Chief, Division of Preventive Medicine, Brigham and
Primary and Secondary Prevention of Coronary Heart Disease

DANIEL B. MARK M.D., M.P.H.

Professor of Medicine, Duke University Medical Center; Director, Outcomes Research and Assessment
Carolina
Economics and Cardiovascular Disease

BARRY J. MARON M.D.

Director, Cardiovascular Research Division, Minneapolis Heart Institute Foundation, Minneapolis, MN
Cardiovascular Disease in Athletes

KENNETH L. MATTOX M.D.

Professor and Vice Chairman, Department of Surgery, Baylor College of Medicine; Chief of Staff and
Traumatic Heart Disease

VALLERIE V. McLAUGHLIN M.D.

*Assistant Professor of Medicine, Rush Medical College; Associate Director, Rush Heart Institute, Cook
Medical Center, Chicago, Illinois
Cor Pulmonale*

JOHN M. MILLER M.D.

Professor of Medicine, Indiana University School of Medicine; Director, Clinical Cardiac Electrophysiology
Management of the Patient with Cardiac Arrhythmias

DOUGLAS N. MINIATI M.D.

Postdoctoral Research Fellow, Department of Cardiothoracic Surgery, Stanford University School of
Heart and Heart-Lung Transplantation

DAVID M. MIRVIS M.D.

Professor of Preventive Medicine and Medicine, University of Tennessee; Director, The Center for

Physical Examination of the Heart and Circulation

WILLIAM S. PIERCE M.D.

Evan Pugh Professor of Surgery, The Pennsylvania State University College of Medicine; The Milton S. Eisenhower Center for Research in Artificial Organs, Hershey, Pennsylvania
Treatment of Heart Failure: Assisted Circulation

JEFFREY J. POPMA M.D.

Associate Professor of Medicine, Harvard Medical School; Director, Interventional Cardiology, Brigham Young University School of Medicine
*Coronary Arteriography;
Percutaneous Coronary and Valvular Intervention*

J. DAVID PORT Ph.D.

Associate Professor of Medicine/Cardiology and Pharmacology, University of Colorado Health Sciences Center
Treatment of Heart Failure: Pharmacological Methods

REED E. PYERITZ M.D., Ph.D.

Professor of Human Genetics, Medicine, and Pediatrics and Chair, Department of Human Genetics, University of Colorado Health Sciences Center
Genetics and Cardiovascular Disease

BRUCE A. REITZ M.D.

Professor and Chairman, Department of Cardiothoracic Surgery, Stanford University School of Medicine
Heart and Heart-Lung Transplantation

STUART RICH M.D.

Professor of Medicine, Rush Medical College; Director, Rush Heart Institute Center for Pulmonary Hypertension, Rush University Medical Center, Chicago, Illinois
*Pulmonary Hypertension;
Cor Pulmonale*

WAYNE E. RICHENBACHER M.D.

Professor of Surgery and Anatomy and Cell Biology and Professor, Division of Cardiothoracic Surgery, University of California, San Diego
Treatment of Heart Failure: Assisted Circulation

PAUL M RIDKER M.D., M.P.H.

Associate Professor of Medicine, Harvard Medical School; Director of Cardiovascular Research, Brigham Young University School of Medicine
Boston, Massachusetts
Risk Factors for Atherosclerotic Disease; Primary and Secondary Prevention of Coronary Heart Disease

ROBERT C. ROBBINS M.D.

Assistant Professor, Department of Cardiothoracic Surgery, Stanford University School of Medicine
University Medical Center, Stanford, California
Heart and Heart-Lung Transplantation

MICHAEL RUBART M.D.

ROBERT SOUFER M.D.

Associate Professor of Medicine, Yale University School of Medicine; Attending Physician and Chief of Nuclear Cardiology, Care Systems, West Haven, Connecticut
Nuclear Cardiology

**DAVID H. SPODICK M.D.
D.Sc.**

Professor of Medicine, University of Massachusetts Medical School; Director of Clinical Cardiology Center/St. Vincent's Hospital, Worcester, Massachusetts
Pericardial Diseases

ROBERT M. STEINER M.D.

Professor of Radiology, Weill Medical College of Cornell University; Attending Radiologist, New York Presbyterian Hospital
Radiology of the Heart and Great Vessels

RICHARD M. STONE M.D.

Associate Professor of Medicine, Harvard Medical School; Clinical Director, Adult Leukemia Program, Dana-Farber Cancer Hospital, Boston, Massachusetts
Hematological-Oncological Disorders and Cardiovascular Disease

JUDITH THERRIEN M.D.

Assistant Professor of Medicine, McGill University; Co-Director of Adult Congenital Heart Disease Program, St. Justine's Hospital, Quebec, Canada
Congenital Heart Disease in Adults

FRANS J. TH. WACKERS M.D.

Professor of Diagnostic Radiology and Medicine and Director, Cardiovascular Nuclear Imaging and Intervention, Yale-New Haven Hospital, New Haven, Connecticut
Nuclear Cardiology

MATTHEW J. WALL JR. M.D.

Associate Professor of Surgery, Department of Surgery, Baylor College of Medicine, Houston, Texas
Traumatic Heart Disease

GARY D. WEBB M.D.

Professor of Medicine, University of Toronto; Director, University of Toronto Congenital Cardiac Center
Congenital Heart Disease in Adults

GORDON H. WILLIAMS M.D.

Professor of Medicine, Harvard Medical School; Director, Clinical Research Center, and Chief, Endocrine Unit, Massachusetts General Hospital, Boston, Massachusetts
The Heart in Endocrine Disorders

JOSHUA WYNNE M.D., M.B.A.

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Publisher's Note

We are proud to announce that two distinguished cardiologists, Drs. Douglas P. Zipes and Peter Libby, have joined the editorial team. Dr. Zipes is a world-renowned arrhythmologist and clinical electrophysiologist, and Dr. Libby is a leading expert in the field of atherosclerosis. Both are heads of important Divisions of Cardiology with strong academic and clinical programs.

Preface

The accelerating advances in cardiology since the publication of the fifth edition of *Heart Disease* have been remarkable. This edition, the first in the new millennium, contains 30 chapters that are new (the most for any revision) and updated. The editors warmly welcome 56 authors who are new to this edition.

Cardiovascular disease is now, more than ever, a global problem with enormous economic consequences. New approaches and cultures are presented in the new opening chapter by Gaziano, and principles of cost-effective medicine are discussed. The Examination of the Patient, begins with the clinical examination and moves progressively from the physical examination to the laboratory. All of these approaches are described in detail with many new illustrations. The new chapter "Relationships of Cardiac Disease to Other Organ Systems" provides a rational approach to the selection among several methods available to image the heart.

Heart failure is becoming an increasingly prevalent problem. Bristow has prepared two new chapters on medical and surgical options based on pathophysiological considerations. There also has been enormous progress in cardiac transplantation. A cadre of talented authors to help update this section, always one of the strongest in *Heart Disease*.

The section on atherosclerosis is entirely new, reflecting greatly expanded information in this field and the development of atherosclerosis and methods for its prevention are presented in new chapters. In vascular disease, a new chapter on diabetes mellitus and cardiovascular disease has been added. In the section on extracardiac vascular disease. In new chapters on this subject, Creager and Libby describe the diagnosis and treatment of peripheral vascular disease. Samuels describe the extracardiac vascular interventions.

The acute coronary syndromes are, by far, the most common diagnoses for cardiovascular patients. Cannon and Braunwald describe the many new diagnostic techniques and therapeutic measures available. They provide a detailed contemporary description of the clinical manifestations and management of acute coronary syndromes.

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Adapted from the Preface to the

Cardiovascular disease is the greatest scourge affecting the industrialized nations. As with previous smallpox--cardiovascular disease not only strikes down a significant fraction of the population with an even larger number. In the United States alone, despite recent encouraging declines, cardiovascular disease is the leading cause of death and more than half of all deaths; almost 5 million persons afflicted with cardiovascular disease are suffering and the cost to human suffering and of material resources is almost incalculable. Fortunately, research focusing on the prevention and treatment of cardiovascular disease is moving ahead rapidly.

In order to provide a comprehensive, authoritative text in a field that has become as broad and deep as it is, I have sought the help of able colleagues. However, I hoped that my personal involvement in the writing of about half of the text would help to overcome the inconsistencies, organizational difficulties, and impersonal tone that sometimes plague multiauthor works.

Since the early part of the 20th century, clinical cardiology has had a particularly strong foundation. In addition to the traditional disciplines of anatomy, physiology, and pathology, recently, the disciplines of molecular biology, genetics, developmental biology, biophysics, biochemistry, and immunology have been added to provide critically important information about cardiac function and malfunction. Although *Heart Disease* is a treatise and not a textbook of fundamental cardiovascular science, an effort has been made to explain the basic principles of the field.

EUGENE BRAUNWALD, 1980

NOTICE

Medicine is an ever-changing field. Standard safety precautions must be followed, but as new research and treatment and drug therapy may become necessary or appropriate. Readers are advised to check the package insert of each drug to be administered to verify the recommended dose, the method and duration of administration, and the contraindications. The author and publisher, relying on the judgment of the treating physician, relying on experience and knowledge of the patient, to determine dosages and administration. The editor assumes no liability for any injury and/or damage to persons or property arising from the use of the information contained herein.

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Part I - GENERAL CONSIDERATIONS OF CARDIOVASCULAR DISEASE

1

Chapter 1 - Global Burden of Cardiovascular Disease

J. MICHAEL GAZIANO

THE EPIDEMIOLOGICAL TRANSITIONS

At the beginning of the 20th century, cardiovascular disease (CVD) accounted for less than 10 percent of all deaths in the developed world and 25 percent in the developing world.^{[1] [2]} By 2020, CVD (CHD) will surpass infectious disease as the world's number one cause of death and disability.

This global rise in CVD is the result of a dramatic shift in the health status of individuals around the world. There has been an unprecedented transformation in the dominant disease profile, or the distribution of diseases. In 1900, infectious diseases and malnutrition were the most common causes of death. These have been replaced by chronic diseases such as CVD and cancer, thanks largely to improved nutrition and public health measures. In developed countries, CVD will dominate as the major cause of death by 2020, accounting for at least one in every five deaths.

This shift in the diseases that account for the lion's share of mortality and morbidity is known as the epidemiological transition. It occurs in isolation but is tightly intertwined with changes in personal and collective wealth (economic development) and population structure (demographic transition).

Because the epidemiological transition is linked to the evolution of social and economic forces, it has occurred and is occurring in every part of the world, at the beginning of the 20th century and by region. For example, life expectancy in Japan (80 years) is more than twice that in Sierra Leone (38 years). Murray and Lopez in their comprehensive analysis of the global burden of disease--communicable, reproductive, and maternal conditions, and injuries and violence--found that in 1990, just 6 percent of deaths in so-called developed countries compared with 33 percent in India.^[2] The vast majority of these deaths occurred in three broad economic and geographical sectors of the world (Table 1.1). These include the catch-up

The Age of Pestilence and Famine

From the epidemiological standpoint, humans evolved under conditions of pestilence and famine and were characterized by the predominance of malnutrition and infectious disease and by the infrequency of epidemics. In pre-market economies, the transition through the age of pestilence and famine was relatively slow, beginning in the 18th century. Competing influences prolonged the transition--improvements in the food supply early in the Industrial Revolution were offset by increases in communicable disease such as tuberculosis, cholera, dysentery, and influenza.

Although the transition through the age of pestilence and famine occurred much later in the emerging market economies, it taken place more rapidly, driven largely by the transfer of low-cost agricultural products and technological advances. Much of the developing world has emerged from the age of pestilence and famine. In sub-Saharan Africa, infectious disease remain leading causes of death.

TABLE 1-2 -- FOUR TYPICAL STAGES OF THE EPIDEMIOLOGICAL TRANSITION

| STAGE | DESCRIPTION |
|------------------------------------|--|
| Pestilence and famine | Predominance of malnutrition and infectious diseases as causes of death; high rates of infant and child mortality; low mean life expectancy |
| Receding pandemics | Improvements in nutrition and public health lead to decrease in rates of death due to malnutrition and infection; precipitous decline in infant and child mortality rates |
| Degenerative and man-made diseases | Increased fat and caloric intake and decreased physical activity lead to emergence of hypertension and atherosclerosis; with increased life expectancy, mortality from chronic, noncommunicable diseases exceeds mortality from malnutrition and infectious diseases |
| Delayed degenerative diseases | Cardiovascular diseases and cancer are the major causes of morbidity and mortality; better treatment and prevention efforts help avoid deaths among those with disease and delay primary events. Age-adjusted CVD mortality declines as life expectancy increases, affecting older and older individuals |

CHD=coronary heart disease; CVD=cardiovascular disease.

Adapted from Omran AR: The epidemiologic transition: A theory of the epidemiology of population change. Am J Public Health 1971;61:958-964. Ault AB: The fourth stage of the epidemiologic transition: The age of delayed degenerative diseases. JAMA 1988;260:1023-1026.

The Age of Receding Pandemics

Rising wealth and the resultant increase in the availability of food help usher in the second phase of the epidemiological transition. Deaths due to malnutrition and may also reduce susceptibility to infectious diseases. Increased public health measures that contribute to still further declines in infectious diseases. These advances, in turn, help improve the economic situation. The change most characteristic of this phase is a precipitous decline in infant and child mortality and a corresponding increase in life expectancy. Examples of countries in this phase of the epidemiological transition are the United States and Japan. In these countries, approximately 29 percent of deaths are due to CVD and only 16 percent are due to communicable diseases. Lower rates of communicable, maternal, perinatal, and nutritional diseases eventually lead to

The Age of Degenerative and Man-Made Diseases

the prevalence of CVD increases as the population ages.

Economic, Social, and Demographic Transitions

As mentioned earlier, several parallel transformations accompany the epidemiological transition. The way for major shifts in a population's health and the nature of the diseases that account for most are characterized by increasing per capita income; the social transition by industrialization and the resulting wider access to health care, and increasing application of health technologies; and the demographic transition leading to increases in life expectancy and an aging population.

ECONOMIC TRANSITION.

This is measured by rising levels of personal wealth, usually measured as per capita gross domestic product.

SOCIAL TRANSITION.

Industrialization tends to spark a large number of social changes. It is typically accompanied by urbanization and the epidemiological transition. Urbanization affects living standards and life style and affords the opportunity for better health care.

In virtually every region of the world there has been a shift from rural to urban life. For example, in the United States at the beginning of the 20th century compared with only 20 percent at the beginning of the 21st century (Fig. 1-2).

Figure 1-1 Increase and decline in heart disease rates through the epidemiological transition in the United States, 1900-1999. Diseases are classified according to International Classification of Diseases (ICD) codes in use when the data were collected (1939, 1949, 1958, 1968, and 1979). Death rates before 1933 do not include all states. Comparability ratios were applied to rates before 1933. *Decline in deaths from heart disease and stroke--United States, 1900-1999. MMWR Morbid Mortal Wkly Rep 48:649-654.*

DEMOGRAPHIC TRANSITION.

This refers to the shifting age structure of a population. During the age of pestilence and famine, infant mortality is high and the population is young. As child and infant mortality are reduced in the age of receding pandemics, rapid gains in life expectancy at 20 and younger decreases. Declines in mortality rates are generally followed by declining fertility rates. As population growth rates fall, the mean age of the population continues to rise slowly as individuals live longer.

RATE OF CHANGE OF THE EPIDEMIOLOGICAL TRANSITION

Several factors influence how early or how quickly the epidemiological transition occurs in a given country. The rate at which a population may undergo the transition at varying rates. These factors are related to economic, social, and cultural changes.

CLASS.

Epidemiological transitions occur at different rates across economic groups, generally beginning among those with higher socioeconomic status and spreading to those with lower socioeconomic status. The decline in rates of malnutrition and communicable diseases occur first in the privileged classes; increases in rates of stroke and CHD soon follow. Later, the transition spreads to a broad enough sector of the population to have a measurable impact on population rates. Through the second and third phases of the transition, CVD and cancer rates become the population's leading causes of death. In the lower socioeconomic strata tend to acquire the risk factors and behaviors last, in part because of their economic conditions and less physical activity at work. Compared with people in the upper and middle socioeconomic strata, those in the lower strata have less access to health care, treatments and to acquire and apply information on modification of risk factors and behaviors. Thus, the transition occurs at different rates across socioeconomic groups.

meat-packing plants were established in or near urban areas. As a result, consumption of fresh fruit increased, resulting in diets that were higher in fat and processed carbohydrates.^[10] In addition, the

TABLE 1-3 -- TRENDS IN THE UNITED STATES DURING THE 20TH CENTURY

| | 1900 |
|---|-------------|
| Population (millions) | 76 |
| Per Capita Income (in 1997 dollars) | NA |
| Age-Adjusted CVD Mortality/100,000 | 325 |
| Age-Adjusted CHD Mortality/100,000 | NA |
| Age-Adjusted Stroke Mortality/100,000 | 140 |
| Urbanization | 39.6% |
| Life Expectancy | 49.2 |
| Smoking | |
| Cigarettes per capita | 54 |
| % Smokers | NA |
| Total Caloric Intake | 3500 kcal |
| Fat Intake (% of total calories) | 31.6% |
| Cholesterol Level | NA |
| % Overweight | NA |
| NA=Not available. | |
| <i>Sources:</i> | |
| Population: US Census Bureau. | |
| Per capita income: U.S. Bureau of the Census: Current Population Reports, P60-203, Measuring 50 Years of Progress. Washington, DC, U.S. Government Printing Office, 1998. | |
| CVD, CHD, stroke mortality: NHLBI Chartbook 1998, MMWR. | |
| Urbanization: 1990 Census of Population and Housing, "Population and Housing Unit Counts," CPUS-90-1. | |
| Life expectancy: National Center for Health Statistics. US decennial life tables for 1989-1991, some preliminary. Hyattsville, Maryland; 1999 (DHHS-99-1150-3). | |
| Smoking: per capita consumption from Surgeon General 1989; % smokers from National Health Interview Survey. | |
| Total caloric intake: Nutrient content of the US food supply, 1909-1994: a summary. USDA; 1998. | |
| Fat intake: Nutrient content of the US food supply, 1909-1994: a summary. USDA; 1998. | |
| Energy expenditure: National Center for Health Statistics. | |
| Cholesterol level: MMWR 48:649-656, 1999. | |
| % obesity: MMWR 1999; 48:649-656, 1999. | |

cigarettes made them more portable and more affordable for the mass population.^[11]

EMERGENCE OF A PUBLIC HEALTH INFRASTRUCTURE.

By 1900, such an infrastructure had emerged--40 states had health departments and many larger towns had sewerage systems.^[9] Municipal use of chlorine to disinfect water was becoming widespread, and impurities were being removed.^[12] The health care system was growing but still largely comprised general practitioners and was largely indigent. The Flexner Report of 1910, which took a careful look at the quality of medical education in the United States, called for quality improvement in health care manpower that, along with other public health changes, was responsible for the

approximately 2 percent per year, and stroke rates have fallen 3 percent per year (see [Fig. 1-1](#)) . T complete statistics are available.

DECLINE IN CVD MORTALITY.

Two main factors have been attributed to the decline in CVD mortality rates--therapeutic advances potentially at risk for it.^{[18] [19]} Treatments once considered advanced, including the establishment of widespread use of new diagnostic and therapeutic technologies such as defibrillation, cardiac catheterization, and bypass surgery, are now considered the standard of care. Advances in the pharmaceutical industry for primary prevention. Efforts to improve the acute management of myocardial infarction led to the development of angiotensin-converting enzyme inhibitors (see [Chap. 35](#)) .^[20] The widespread use of an "old" drug, aspirin, for the prevention of coronary events. Low-cost pharmacological treatment for hypertension (see [Chap. 29](#)) and the development of statins have also made major contributions

Figure 1-4 Decline in mortality due to infectious diseases in the United States, 1900 to 1996. Rate is per 100,000 population. Water chlorination principles and practices: AWWA manual M20. Denver, American Water Works Association, 1973. (Adapted from *MMWR Morbid Mortal Wkly Rep* 48:621-629, 1999. Adapted from Armstrong GL, Conn LA, Pinner RW: Trends in infectious diseases. *MMWR* 281:61-66, 1999.)

TABLE 1-4 -- CARDIOVASCULAR DISEASE, UNITED STATES, 1996

| TYPE | PREVALENCE* (MILLION) | CRUDE MORTALITY RATE* (THOUSANDS PER 100,000 PER YEAR) |
|---------------------------------|----------------------------------|---|
| Cardiovascular disease | 59.7 | 296.0 |
| Hypertension | 50 | 29 |
| Ischemic heart disease | 12.2 | 466 |
| Stroke | 4.4 | 160 |
| Arrhythmia | 3.9 | 45 |
| Congestive heart failure | 4.6 | 49 |
| Rheumatic heart disease | 1.8 | 5 |
| Valvular disease (nonrheumatic) | NA | 17.6 |
| | ANNUAL EVENTS* (THOUSAND) | |
| Myocardial infarction | 1100 | |
| New | 650 | |
| Recurrent | 450 | |
| Stroke | 600 | |
| New | 500 | |
| Recurrent | 100 | |
| CABG | 607 | |
| PTCA | 447 | |
| Valve surgery | 78 | |
| Total costs | | |
| Direct | \$185.8 billion | |

no change in stroke rates for the last 5-year period for which data are available. The rate of decline of decline in risk factors such as smoking and increases in other risk factors such as obesity.

CURRENT WORLDWIDE VARIATIONS IN THE GLOBAL BURDEN OF CVD

An epidemiological transition much like the one that occurred in the United States is occurring throughout the world. It has risen steadily throughout the 1900s. At the close of the 20th century, 28 percent of all deaths worldwide were due to CVD, up from 18 percent in 1990 and 12 percent in 1970. By 2020, CVD is projected to account for 34 percent of the total.^[2] With the ongoing global transition--dominated by the transition in the developed world--CVD is projected to account for 36.3 percent of all deaths in 2020, whereas communicable diseases will account for 16.3 percent.

Looking behind the global transition reveals vast discrepancies in regional rates of change. These variations are due to the fact that most of the world remained in the phase of pestilence and famine, economic circumstances in severe poverty, and a slow pace of their epidemiological transitions. Thus, the global burden of CVD is best understood by examining regional variations. In addition to variability in the rate of the transition, there are unique regional features that have modified the transition.

In terms of economic development, the world can be divided into two broad sectors, as described in Table 1-1. The world is subdivided into the established market economies (EstME) and the emerging market economies (EmgME). Within the EmgME, there is diversity within the DevE, it is useful to further subdivide it into six distinct economic/geographic regions: sub-Saharan Africa, the Middle Eastern Crescent, and Latin America and the Caribbean. In 2000, 40 percent of the world's population lived in these countries, and it is these countries that are driving the rates of change in the global burden of CVD.

Like the United States, the rest of the EstME are largely in the fourth phase of the epidemiological transition, with CVD and communicable diseases accounting for well under 10 percent (see Table 1-1). The EmgME are in the third phase, with CVD accounting for 10 percent of deaths. In the DevE overall, 23 percent of deaths are due to CVD, whereas communicable diseases account for 10 percent. In subgroups of the DevE, however, there remains a high degree of heterogeneity with respect to the dominant disease rates in each region (Table 1-5). In sub-Saharan Africa, communicable disease rates are high (third phase, pestilence and famine). Some regions of India appear to be in the first phase, characterized by high rates of communicable disease, while others are in the second or even the third phase. The Middle East appears to be in the third phase of the transition, but the difficulties

TABLE 1-5 -- PERCENT MORTALITY AND PERCENT DISABILITY-ADJUSTED LIFE YEARS

| DEATHS | | China | India |
|-------------------------|--|-------|-------|
| CMPN | | 15.8 | 5.0 |
| Injury | | 11.5 | 3.0 |
| NonCVD, nonCMPN | | 43.8 | 1.0 |
| All CVD | | 28.9 | 2.0 |
| Ischemic heart disease | | 8.6 | 1.0 |
| Stroke | | 14.3 | 1.0 |
| Rheumatic heart disease | | 1.8 | 0.0 |
| Other CVD | | 3.4 | 0.0 |
| DALYs | | | |
| CMPN | | 24.2 | 5.0 |
| Injury | | 17.6 | 1.0 |
| NonCVD, nonCMPN | | 47.2 | 2.0 |
| All CVD | | 11.0 | 3.0 |
| Ischemic heart disease | | 2.9 | 3.0 |
| Stroke | | 5.2 | 0.0 |
| Rheumatic heart disease | | 1.1 | 0.0 |

| | |
|--------------------------------|------|
| Women | 552 |
| Portugal | |
| Men | 1673 |
| Women | 805 |
| Finland | |
| Men | 1691 |
| Women | 1718 |
| Scotland | |
| Men | 1846 |
| Women | 1103 |
| Economies in Transition | |
| Russian Federation | |
| Men | 2881 |
| Women | 1223 |
| Ukraine | |
| Men | 2940 |
| Women | 1379 |

CVD=cardiovascular disease; CHD=coronary heart disease.

World Heart Federation: Impending Global Pandemic of Cardiovascular Diseases. Barcelona, Pro

much greater. For example, male CHD rates are 362 percent higher in Finland than in Spain, where New Zealand, and Australia are similar to those in the United States.

JAPAN.

This country is unique among the EstME. As its rates of communicable disease fell in the early part of the middle of the century they were the highest in the world. CHD rates, however, did not rise as sharply as in other industrialized countries. Overall CVD rates have fallen 60 percent since the 1960s. Japanese men and women currently have the highest life expectancies in the world--83 years for men and 87 for women. Other industrialized countries may stem from genetic factors, but it is more likely that the average value of life expectancy is more important. As is true for so many countries, Japanese dietary habits are undergoing substantial changes. There has been an increase in annual per capita consumption of meat between 1955 and 1994, a 5.2-fold increase in consumption of fats and oils.^[28] These changes may explain possible recent trends in CVD mortality.

Emerging Market Economies

The EmgME currently have the highest rates of CVD mortality in the world, and they are continuing to rise. They are largely in the third phase of the epidemiological transition. In the former Soviet and Eastern Bloc countries, CVD accounting for approximately 54 percent of deaths, whereas communicable diseases account for only 10 percent. The average age of people who develop and die of CVD is lower than that in the established market economies.

Overall rates are similar to those seen in the United States in the 1960s, when CVD was at its peak. The ratio of CVD mortality is relatively low, approximating 1:1 in several countries. Within the EmgME, CVD mortality rates vary widely (1,343 for men and 830 for women per 100,000) and Russia (1,343 and 657), and the lowest rates are in South Africa (1,000 for men and 500 for women) compared with rates in EstME countries.

FORMER SOVIET UNION COUNTRIES.

China has doubled from 35 years to 70 years. Over the same period, mortality from CVD increased

As in Japan, stroke is by far the leading cause of cardiovascular death. Hemorrhagic stroke predominates among women than men. These lower rates of CHD and high rates of stroke may be due to genetic factors. High cholesterol levels may contribute to high rates of hemorrhagic stroke.^[31] There appears to be a north-south gradient with southern China. As is the case in most DevE, there is also an urban/rural gradient for CHD, stroke, and other CVD. Differences exist in CVD rates, although they are not as great as those seen in India and sub-Saharan Africa, which results in less regional differences in the standard of

TABLE 1-7 -- RHEUMATIC HEART DISEASE, MORTALITY

| REGION | NUMBER OF DEATHS (THOUSAND) | % OF CVD |
|--------------------------|-----------------------------|----------|
| EstME | 21 | 0 |
| EmgME | 26 | 1 |
| DevE | 338 | 2 |
| India | 80,000 | 2 |
| China | 192,000 | 5 |
| Other Asia | 13,000 | 0 |
| Sub-Saharan Africa | 19,000 | 1 |
| Middle East Crescent | 25,000 | 1 |
| Latin America, Caribbean | 9,000 | 0 |

CVD=cardiovascular disease; DALYs=disability-adjusted life years; EstME=established market economies.

Adapted from Murray CJL, Lopez AD: The Global Burden of Disease. Cambridge, MA, Harvard School of Public Health, 1996.

living compared with Africa or India. In general, China appears to be in the third stage of a Japanese transition, although dominated by stroke and not CHD as they are in the EstME and EmgME. Major features of the transition are smoking and hypertension, much of which remains untreated.

INDIA.

One sixth of the world's population lives in India, with 72 percent of the approximately 1 billion people living in urban areas. Cause-specific mortality are not available; the most reliable data derive from urban centers. The best available data show 1.2 million deaths.^[2] As expected, CVD mortality rates tend to be higher in urban areas than rural areas and CVD is the leading cause of death.

In contrast to China and much of the rest of Asia, CHD appears to be the dominant form of CVD. In 1990 the proportion was over 50 percent.^[32] CHD death rates are currently about three times higher than stroke. CHD tends to be a more dominant factor early in the epidemiological transition. This may reflect inaccurate data or metabolic differences in response to the Western life style of higher-fat diets and lower levels of activity. Insulin insensitivity in response to this life-style pattern that may differentially increase rates of CHD. Dairy consumption, much of which comes from dairy products, is significantly higher in India than in other parts of the developing world.

Although rates of communicable disease remain high, accounting for 51 percent of all deaths and 51 percent of DALYs, India appears to be early in the second phase of the transition with the urban upper classes in the third phase. CHD is the leading cause of morbidity and mortality (see [Table 1-7](#)). Certain remote areas, however, are still in the agricultural phase, accounting for 10 percent of total deaths.^[33]

SOUTHEAST ASIA.

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