
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

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W.B. SAUNDERS COMPANY

A Harcourt Health Sciences Company

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W.B. SAUNDERS COMPANY

A Harcourt Health Sciences Company

The Curtis Center

Independence Square West

Philadelphia, Pennsylvania 19106

Library of Congress Cataloging-in-Publication Data

Heart disease: a textbook of cardiovascular medicine[edited by] Eugene Braunwald, Douglas P. Zipes, Peter Libby.--6th ed.

p. cm.

Includes bibliographical references and index.

ISBN 0-7216-8561-7

1. Heart--Diseases. 2. Cardiovascular system--Diseases. I. Braunwald, Eugene. II. Zipes, Douglas P. III. Libby, Peter. [Heart disease: a textbook of cardiovascular medicine. WG 210 H43445 2001]

RC681. H36 2001 616.1'2--dc21 00-025391

Editor-in-Chief: Richard Zorab

Developmental Editor: Lynne Gery

Manuscript Editors: Sue Reilly, Anne Ostroff

Production Manager: Frank Polizzano

Illustration Specialist: Rita Martello

Book Designer: Karen O'Keefe Owens

Heart Disease: A Textbook of Cardiovascular Medicine

0-7216-8549-8 (Single Volume)

0-7216-8561-7 (2-Volume Set)

0-7216-8562-5 (Volume 1)

0-7216-8563-3 (Volume 2)

0-8089-2258-0 (International Edition)

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Printed in the United States of America.

Last digit is the print number: 9 8 7 6 5 4 3 2 1

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

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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 26 chapters that have been revised 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 to diagnosis and cultures are presented in the new opening chapter by Gaziano, and principles of cost-effective management 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 pathogenesis and 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 management 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. The section on acute myocardial infarction provides a detailed contemporary description of the clinical manifestations and management of acute myocardial infarction.

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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 texts.

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 all 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 21st 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, maternal, neonatal, and nutritional 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. New York: Academic Press, 1971; Ault AB: The fourth stage of the epidemiologic transition: The age of delayed degenerative diseases. JAMA 1988;260:203-206.

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 a shift in the leading causes of death.

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 conditions.

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 lower 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 introduced.^[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 secondary 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. N Engl J Med* 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	29
Hypertension	50	466
Ischemic heart disease	12.2	160
Stroke	4.4	45
Arrhythmia	3.9	49
Congestive heart failure	4.6	5
Rheumatic heart disease	1.8	17.6
Valvular disease (nonrheumatic)	NA	
	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 14 percent in 1980. By 2020, accounting for 36.3 percent of all deaths whereas communicable diseases will account for 14.3 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 several regions have retarded the 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, 60 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 23 percent of deaths. In the DevE overall, 23 percent of deaths are due to CVD, whereas communicable diseases account for 14.3 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, indicating a 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	8.0
NonCVD, nonCMPN		43.8	14.0
All CVD		28.9	27.0
Ischemic heart disease		8.6	1.0
Stroke		14.3	4.0
Rheumatic heart disease		1.8	0.0
Other CVD		3.4	5.0
DALYs			
CMPN		24.2	5.0
Injury		17.6	14.0
NonCVD, nonCMPN		47.2	27.0
All CVD		11.0	8.0
Ischemic heart disease		2.9	3.0
Stroke		5.2	4.0
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. CHD rates are lower than in any other industrialized country. 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 a 5.2-fold 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.

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 to all deaths 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 and 500) 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, that 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 55 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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