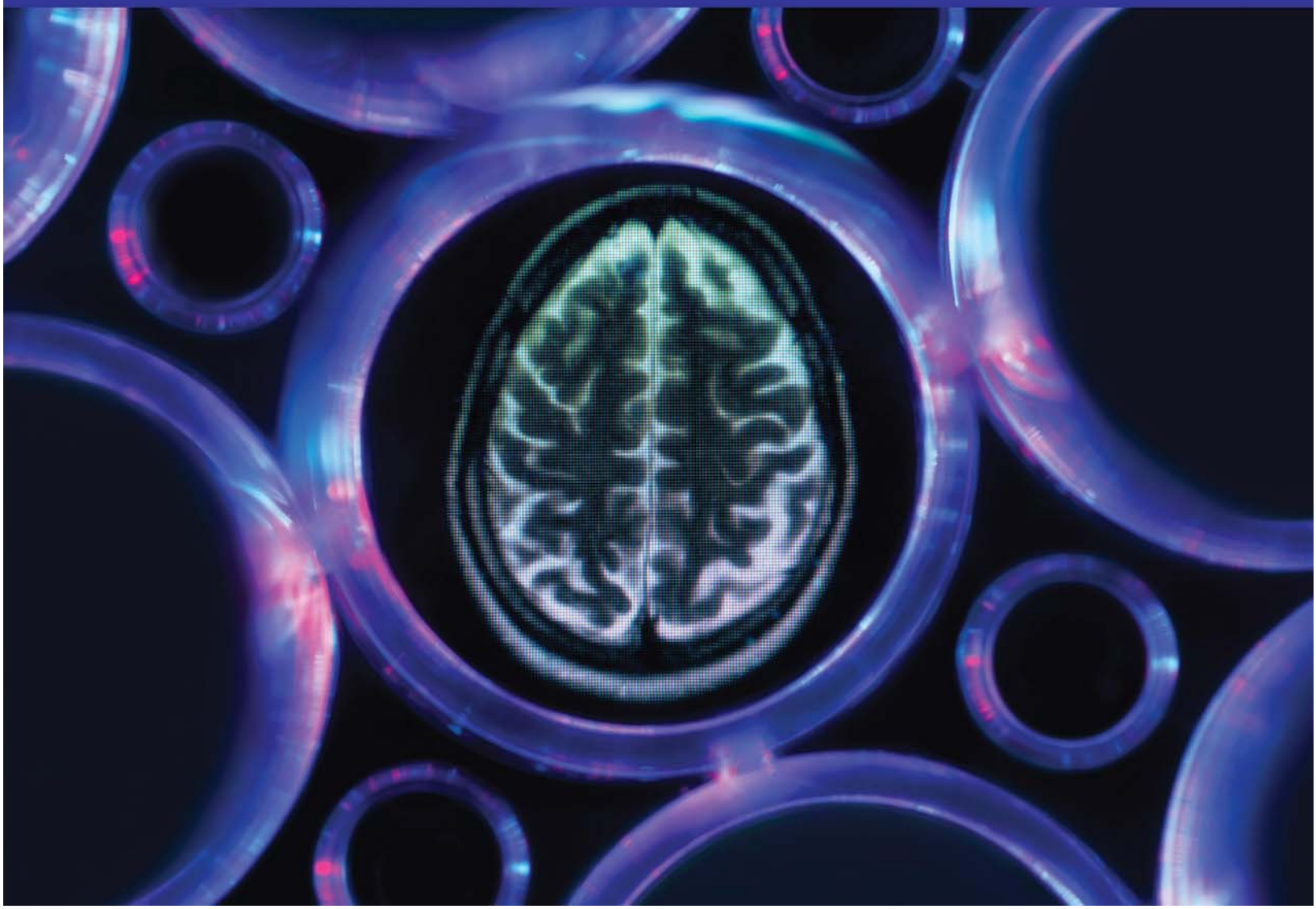
Randall E. Harris

EPIDEMIOLOGY OF CHRONIC DISEASE

Global Perspectives

SECOND EDITION



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Preface

This second edition of *Epidemiology of Chronic Disease: Global Perspectives* is written for all students and teachers of the health sciences, particularly those in epidemiology, public health, and medicine. Its main purpose is to present current and comprehensive information on epidemiology, etiology, pathogenesis, risk factors, and preventive factors of common chronic diseases. In writing the new edition of this book, I have made liberal use of the internet and drawn upon worldwide information to address the global landscape of chronic diseases.

This new edition has 56 chapters that are organized into five distinct sections beginning with an introductory chapter on the "*epidemiologic transition*" whereby chronic diseases have replaced acute infectious conditions concurrent with improved health care and increasing longevity in many populations of the world. Subsequent sections cover cardiovascular and cerebrovascular diseases (coronary heart disease, myocardial infarction, sudden cardiac death, stroke, congestive heart failure, peripheral artery disease and aortic aneurysms, venous thromboembolism and pulmonary embolism, and hypertension), major forms of cancer (lung cancer, laryngeal cancer, head and neck cancer, esophageal cancer, stomach cancer, colon cancer, pancreatic cancer, liver cancer, breast cancer, ovarian cancer, vulvar and vaginal cancer, cervical cancer, prostate cancer, testicular cancer and other male genital cancers, bladder cancer, kidney cancer, sarcoma, malignant melanoma, lymphoma, leukemia, and brain tumors), diseases of the respiratory tract (chronic obstructive pulmonary disease and asthma), metabolic and digestive diseases (diabetes mellitus, obesity, thyroid disease, kidney disease, and liver disease), musculoskeletal diseases (osteoporosis and arthritis), neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, schizophrenia, epilepsy, multiple sclerosis, and suicide), and finally three major infectious diseases (tuberculosis, malaria, and HIV disease) that often manifest as chronic conditions.

I have added new chapters on sudden cardiac death, congestive heart failure, peripheral artery disease and aortic aneurysms, and venous thromboembolism and pulmonary embolism. Important new findings are discussed, such as the association of posttraumatic stress disorder with suicide and the emerging crisis of antibiotic resistance in tuberculosis and other chronic infections. Epidemiologic findings and references have been updated throughout this book.

Each chapter follows a similar format, with subsections describing diagnostic criteria, historical perspectives, the global burden of disease, population differences and time trends in incidence, prevalence, disability and mortality, mechanisms of pathogenesis, risk factors, preventive factors, and opportunities for disease prevention and control. Key epidemiologic studies and findings are presented in chronological order with supporting evidence and references selected to guide readers for further study. It is assumed that students and readers are building on a knowledge base of basic epidemiology and human biology. The text blends the traditional elements of epidemiology with human anatomy, physiology, and molecular biology. The text is accompanied by an online instructor's manual with recommended questions and answers drawn from each of the chapters.

It is my hope that the text will provide a forum for examining current hypotheses regarding chronic disease epidemiology. Subsections of each chapter focus on controversial topics in the epidemiology of each disease. This format facilitates active student discussion of molecular mechanisms of disease pathogenesis and the relevant epidemiologic issues pertaining to the prevention and control of chronic diseases.

In essence, the new edition of this book, like the first, is an amalgamation of a long-standing continuum of the exchange of ideas and information with many colleagues in the fields of medicine, public health, epidemiology, biostatistics, genetics, pathology, and molecular biology. This new edition will continue to reflect my own experiences in medicine, epidemiology, and public health, and I am deeply indebted to mentors, colleagues, and particularly students who have contributed to my education, research, and teaching over the past four decades.

What Is New and Improved?

Epidemiology of Chronic Disease: Global Perspectives, Second Edition presents the current epidemiology and global burden of each of the 56 major diseases. This new edition contains the most recent information available on the epidemiology of major cardiovascular diseases; cancers; respiratory, metabolic, and musculoskeletal conditions; and neurodegenerative diseases complete with updated figures, tables, and global maps. The section on cardiovascular and cerebrovascular disease includes four new chapters on the epidemiology of congestive heart failure, peripheral artery disease and aortic dissection, venous thromboembolism and pulmonary embolism, and sudden cardiac death. The new epidemiology of cancer section contains widely updated materials to provide in-depth information on cancers that affect 28 regions of the body.

- **New Chapters.** The new edition includes 13 new chapters to include more information on Epidemiology of Sudden Cardiac Death (Chapter 5), Epidemiology of Heart Failure (Chapter 7), Epidemiology of Aortic Aneurysm and Dissection (Chapter 8), and Epidemiology of Venous Thromboembolism and Pulmonary Embolism (Chapter 9). There are also nine new chapters on cancer epidemiology including Epidemiology of Laryngeal Cancer (Chapter 14), Epidemiology of Cancers of the Lip, Oral Cavity, and Pharynx (Chapter 15), Epidemiology of Cancer of the Corpus Uteri (Chapter 23), Epidemiology of Vaginal, Vulvar, and Anal Cancer (Chapter 25), Epidemiology of Testicular Cancer (Chapter 27), Epidemiology of Carcinoma of the External Male Genitalia (Chapter 28), Epidemiology of Cancers of the Thyroid and Parathyroid (Chapter 31), Epidemiology of Adrenal Cancer (Chapter 32), and Epidemiology of Nonmelanoma Skin Cancer (Chapter 34).
- **Global Burden of Disease.** This new edition incorporates the most recent data from the World Health Organization, the Institute of Health Metrics and Evaluation, the International Agency for Cancer Research, and other international organizations to characterize important global patterns and trends in the epidemiology of each disease. Updated world maps and figures are used to display global patterns and trends in disease prevalence, incidence, mortality, and disability-adjusted life years.
- **U.S. Burden of Disease.** Each chapter includes a section on the burden of disease in the U.S. population based on current data from the National Institutes of Health, the American Heart Association, the American Cancer Society, and other national organizations.
- **Risk Factors.** Published studies from the recent literature are discussed regarding new findings on risk factors and preventive factors that impact the pathogenesis of disease.
- **Pathogenesis.** Current mechanisms of pathogenesis of each disease are discussed and depicted in each chapter.
- **Disease Prevention and Control.** The most recent and effective programs of disease prevention and control are presented in each chapter.
- **Instructor Resources.** Instructors using the text will have online access to updated lecture slides, outlines, and test banks with answers for each chapter.

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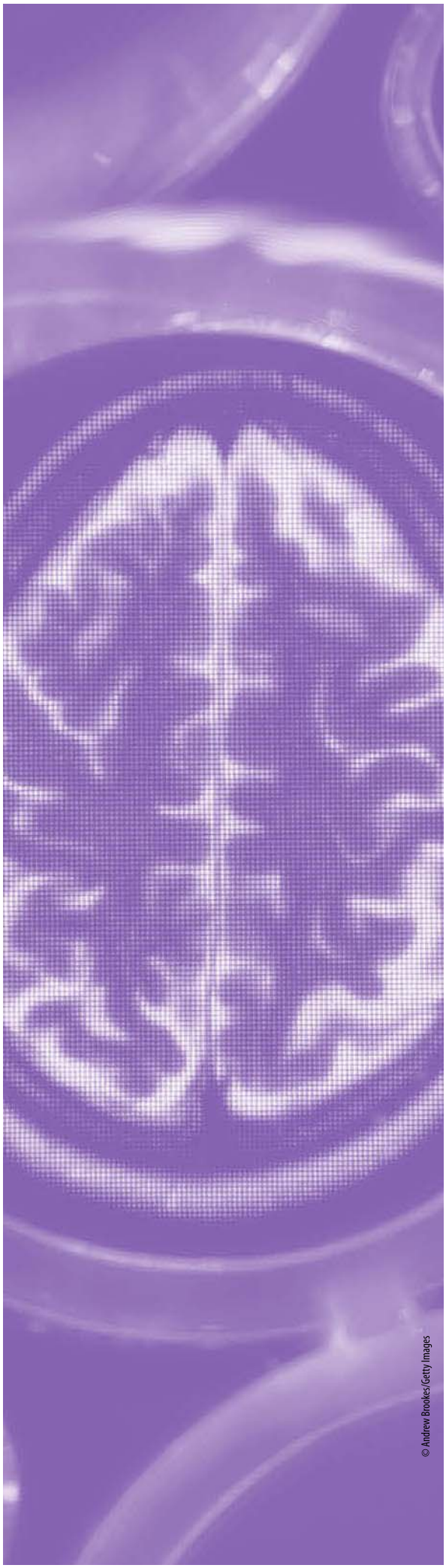
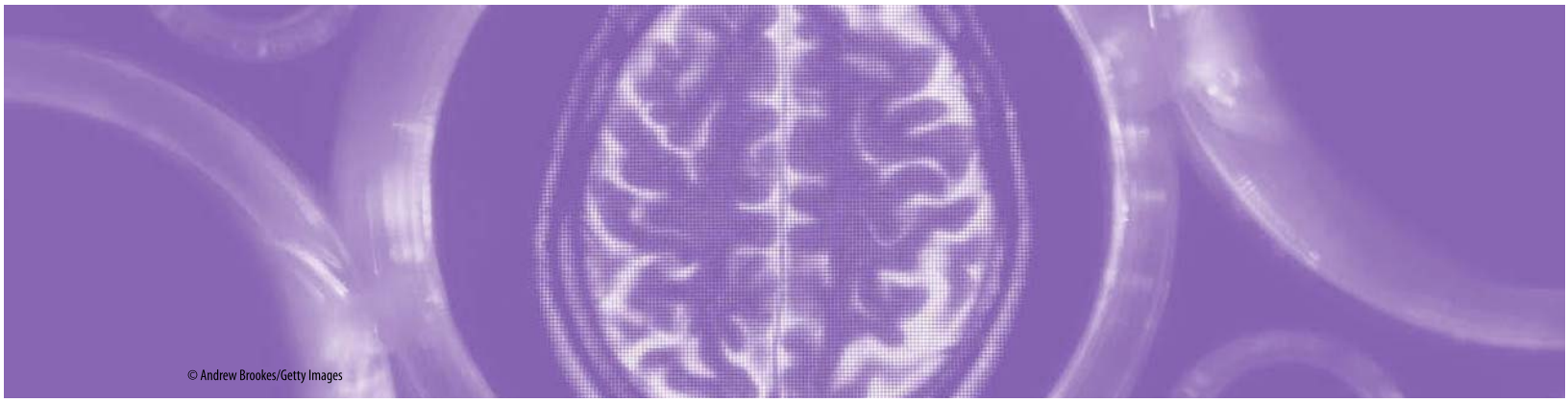


SECTION I

Epidemiologic Transition and Epidemiology of Cardiovascular Diseases



CHAPTER 1

Global Epidemiology of Chronic Diseases: The Epidemiologic Transition

Global Pandemic of Chronic Diseases

A silent pandemic of chronic diseases is gradually enveloping the world population, spreading to all corners of the globe. This distinct spectrum of human afflictions is systemically replacing infectious and parasitic diseases as the leading cause of morbidity and mortality worldwide, thereby producing one of the greatest public health challenges of all time. According to global cause-specific mortality data reported by the *Institute of Health Metrics and Evaluation* noncommunicable (chronic) disorders such as coronary heart disease, stroke, cancer, chronic obstructive pulmonary disease (COPD), diabetes mellitus type 2, neurodegenerative disease, and renal failure accounted for 39.5 million of the 54.7 million deaths (72%) for which a cause was identified during 2016 (Ritchie & Roser, 2018). This compares with 10.6 million deaths (19%) due to communicable (infectious) diseases, maternal, neonatal, and nutritional diseases, and 4.6 million deaths (8%) from injury including homicide, suicide, conflict, and terrorism. As shown in **FIGURE 1.1**, trends in the annual number of deaths in these three categories during 1990–2016 reflect a steady increase in annual deaths from noncommunicable diseases concurrent with a steady decline in annual deaths from communicable, maternal, neonatal, and nutritional diseases, whereas the annual number of deaths from injury has remained stable (Ritchie & Roser, 2018; WHO, 2009a, 2017c).

The following excerpts from the 2008 WHO global report entitled *Preventing Chronic Diseases: A Vital Investment* capture the essence of the global pandemic of chronic diseases (Reprinted from WHO, 2008a).

> *"Chronic diseases are the leading causes of death and disability worldwide. Disease rates from these conditions are accelerating globally, advancing across every region and pervading all socioeconomic classes. The World Health Report 2002 "Reducing Risks, Promoting Healthy Life" indicates that the mortality, morbidity and disability attributed to the major chronic diseases currently account for almost 60% of all deaths and 43% of the global burden of disease. By 2020 their contribution is expected to rise to 73% of all deaths and 60% of the global burden of disease. Moreover, 79% of the deaths attributed to these diseases occur in the developing countries. Four of the most prominent chronic diseases, cardiovascular diseases (CVD), cancer, chronic obstructive pulmonary disease (COPD), and type 2 diabetes, are linked by common and preventable biological risk factors, notably high blood pressure, high blood cholesterol and overweight, and*

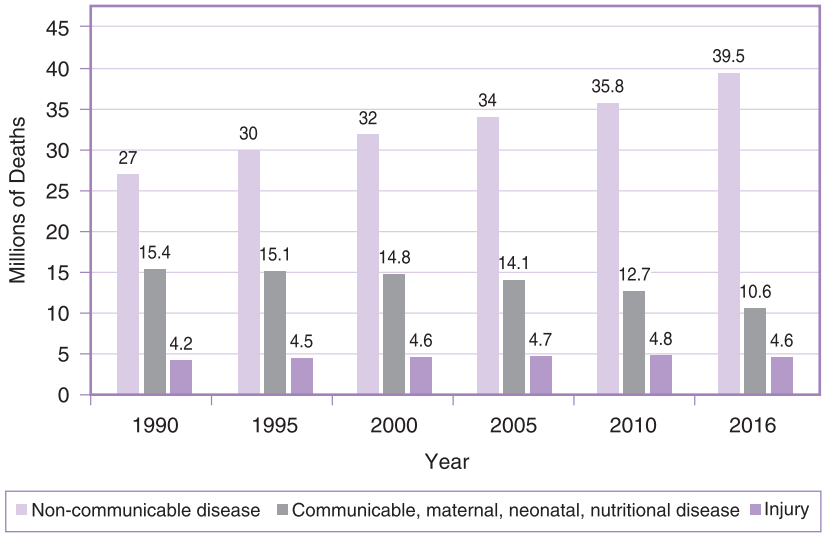


FIGURE 1.1 Global Trends in Deaths from Noncommunicable and Communicable Diseases and Injuries, 1990–2016.

Data from WHO. (2009a). *World health statistics, 2009*. Geneva, Switzerland: WHO; WHO. (2017). *World health statistics, 2017*. Geneva, Switzerland: WHO; Ritchie, H., & Roser, M. (2018). "Causes of Death". Published online at OurWorldInData.org. Retrieved from https://ourworldindata.org/causes-of-death [Online Resource]

by related major behavioral risk factors: unhealthy diet, physical inactivity, and tobacco use. Action to prevent these major chronic diseases should focus on controlling these and other key risk factors in a well-integrated manner."

The global pandemic of chronic diseases has emerged in concert with the changing demography of the world population. Overall, the world birth rate exceeds the death rate, and the number of living individuals on the planet continues to increase. At the same time, more and more people are living to older ages thereby creating the phenomenon of "global aging." Aging populations are particularly evident in the industrialized and developed nations of the world, such as Japan, Italy, and Germany, where the proportion of elderly people (over 65 years of age) has increased from approximately 10% to 20% in the past half century (Hayutin, 2007). In large developing nations such as China and India, the proportion of elderly people is also expected to increase from current levels of about 5% to nearly 10% in the next few decades. In smaller underdeveloped nations where less than 5% of the people currently live beyond 65 years of age, population aging is also progressing, but at a slower pace. As a general consequence of the aging world population, long-term mechanisms of pathogenesis are more likely to cause disease late in life, thus resulting in vastly increased rates of chronic diseases, particularly among the elderly.

Increase in World Population

As of July 1, 2017, The Department of Economic and Social Affairs of the United Nations Secretariat estimated that the world population consisted of 7.55 billion living human beings (World Population Prospects, 2017). In that year, approximately 60 million people died and 140 million new babies were born, a net gain of 80 million people. Based upon projections of death rates and birth rates, the world population is expected to increase to nearly 9 billion people by the year 2040 (**FIGURE 1.2**).

Aging of the World Population

The world population is not only increasing in number, but it is also growing older. Two demographic parameters are driving these phenomena: *longevity is increasing and the fertility rate is decreasing*. Studies at the World Health Organization (WHO, 2009a) and the Stanford Center of Longevity (Hayutin, 2007) clearly show that people around the world are living longer and women are having fewer children.

Increasing Longevity (Life Expectancy)

The average life expectancy (also called longevity) for members of the world population born during 2010–2015 is 71 years (68 years for men and 73 years for women) (CIA, 2017). In the past half century, life expectancy has increased dramatically throughout the world, particularly in populations of developing nations. Since 1950, life expectancy in highly populated nations such as China and India has increased from approximately 40 years to nearly 70 years (**FIGURE 1.3**).

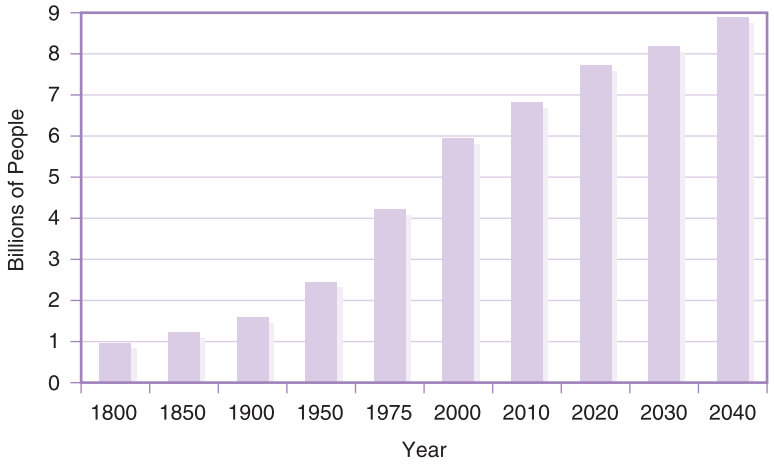


FIGURE 1.2 World Population.

Data from the United States Census Bureau. (2018). International Data Base. (estimates for 2020–2040 are based on curvilinear regression).

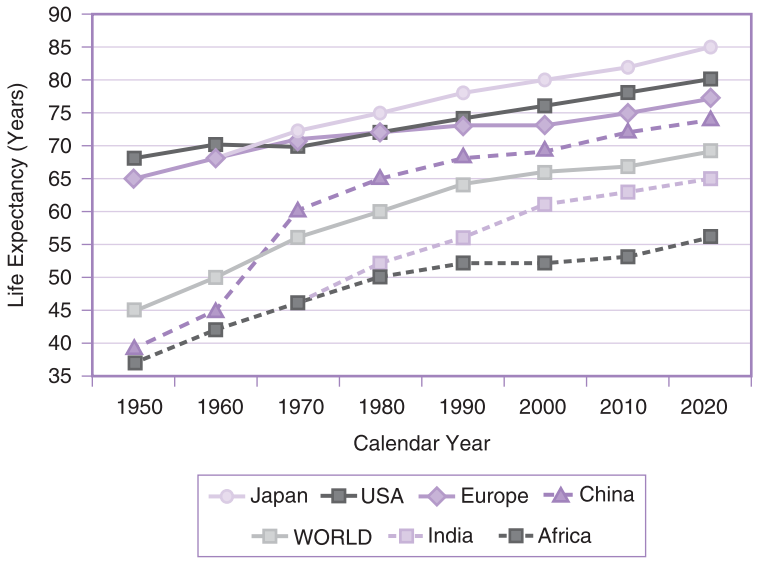


FIGURE 1.3 Longevity Trends in Selected Populations.

Data from United Nations Department of Economic and Social Affairs, Population Division. (2017). *United Nations World Population Prospects: 2017 revision*. New York, NY: United Nations. National Center for Health Statistics, 2017, USA.

In lesser developed nations, particularly those of central Africa where acute infectious and parasitic diseases prevail and greatly reduce the survival of children and young adults, life expectancy is much less, currently only about 50 years. In highly developed nations such as Japan, the United States, and European countries, longevity now approaches or surpasses 80 years and deaths are more likely due to chronic diseases of old age. The Japanese people currently enjoy the greatest longevity, about 82 years. Longevity in the United States currently stands at 79 years, only slightly higher than the average of the more developed nations (**FIGURE 1.4**).

Life expectancy is the average number of years that a newborn could expect to live if he or she were to pass through life *subject to the age-specific death rates of the population of interest for the past year.* Derivation of life expectancy is usually presented as a "*two-step*" process. For large populations, life expectancy is calculated by *first constructing a life table and recording the number of deaths and survivors that occur in a given year for successive intervals of the life span.* The number of deaths and survivors and corresponding age-specific death rates are usually tabulated for ages 0–1 years, 1–5 years, and successive 5-year age groups for ages 5 and above. From these data, a second life table is then constructed to represent the entire mortality experience from birth to death for a hypothetical cohort of 100,000 infants born alive and subject to the age-specific death rates that prevail in the population of interest for a particular year. Using the data from this second life table for 100,000 hypothetical individuals, life expectancy is simply calculated as the average years of life for all members since birth

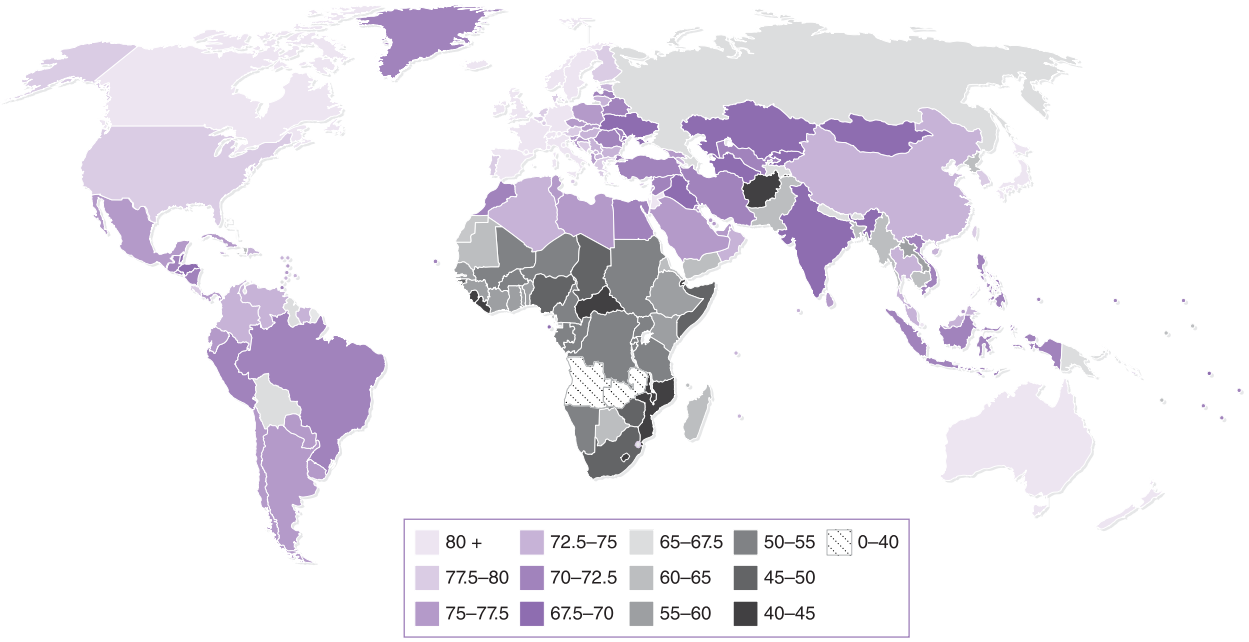


FIGURE 1.4 Global Longevity, 2011.
Data from CIA World Factbook, 2011 Estimates of Life Expectancy at Birth (Years).

(e.g., life expectancy = total years of life for all members of the life table divided by the total number of persons at birth, *Life Expectancy* = Σ *years of life*/*100,000*). Life expectancy (longevity) at birth is therefore the mean years of life for individuals based entirely on the age-specific death rates for the population and year of interest (Colton, 1974).

Gender Differences in Longevity

Throughout the world, life expectancy (longevity) for women is 5–10 years greater than for men. With some exceptions in nations where high maternal death rates prevail due to lack of prenatal care, women have lower death rates and better survival at every age. In the industrialized world, improvements in prenatal care have reduced maternal mortality during the childbearing years thereby widening the gender gap in longevity during much of the 20th century. For example, the gender divergence in longevity in the U.S. population gradually increased from about 2 years in 1900 to approximately 8 years in 1970, after which the difference shrank back to about 6 years, currently 81 years for women versus 75 years for men (**FIGURE 1.5**). The slight shrinkage of the U.S. gender gap during the past 40 years is believed to reflect equalizing smoking rates among men and women (Pampel, 2002).

The survival differential favoring females actually begins at conception. Only about 90% of male fetuses survive to birth compared to nearly 100% of female fetuses. While precise causative factors for this disparity remain unclear, the relatively high rates of spontaneous abortions, miscarriages, and stillbirths among male fetuses could be due to hormonal incompatibilities of the male genotype in a milieu of female hormones such as estrogen and progesterone throughout gestation (Austad, 2006). At the other end of the life span, approximately 70% of individuals over 90 years of age are female, and remarkably, about 90% of centenarians (individuals over 100 years of age) are female (Perls, Hutter Silver, & Lauerman, 1999).

While no single factor can satisfactorily explain the clear survival advantage of women throughout life, certain environmental and biological differences are worth pointing out. The longer life span of women compared to men is undoubtedly related to gender differences in lifestyle. Despite the fact that men are, on average, bigger, stronger, faster, and more economically self-sufficient, their lifestyle choices and risky health behaviors obviously confer a clear survival advantage to women. In general, men have greater exposure to classical risk factors of disease such as tobacco and alcohol and, as a consequence, are more likely to die earlier from associated chronic conditions such as cardiovascular disease, lung cancer, chronic obstructive pulmonary disease, and cirrhosis of the liver. Men are also more likely to die from injuries, whether unintentional (motor vehicle or occupational accidents) or intentional (suicide, homicide, or war). Reciprocally, women have traditionally been the "*sentinels of health*" for their families and communities at large. Due to their instinctive "*nurturing maternal instinct*," women tend to take better care

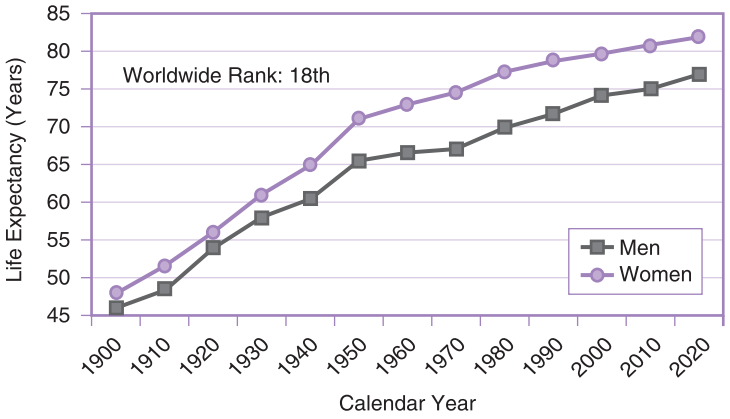


FIGURE 1.5 Life Expectancy, the United States, Women and Men.

Data from United Nations Department of Economic and Social Affairs, Population Division. (2017). *United Nations World Population Prospects: 2017 revision*. New York, NY: United Nations. National Center for Health Statistics, 2017, USA.

of themselves and make healthier lifestyle choices than men, thus contributing to their longer life span.

Hormonal differences between men and women may also influence their differences in lifestyle and longevity. Men are greater risk-takers than women, particularly during the years of young adulthood when circulating levels of testosterone are highest. The biological effects of androgens and estrogens differ dramatically. Androgens have vasoconstrictive and inflammatory effects in blood vessels consistent with higher rates of cardiovascular disease in men whereas estrogens exert opposite effects and are thus cardioprotective in women, particularly during their reproductive years (Blackman et al., 2002; Parker et al., 2009). Moreover, gender differences in the balance of estrogens and androgens appear to confer heightened immunity and more resistance to infectious and degenerative diseases in women throughout life (Austad, 2006).

Aging and Disease

Aging is a complex process involving a decline in physiological processes that are essential for life. As humans age, there is heightened susceptibility to life-threatening acute and chronic diseases. A characteristic "death curve" is depicted in **FIGURE 1.6**. The data points represent approximate all-cause annual mortality rates estimated for successive 10-year age brackets for the U.S. population of 2002 (National Vital Statistics System, 2002). Note that the risk of death is elevated in the early years up to 5 years of age, after which there is a relatively long subtle increase in the risk of death until approximately 40 years of age, after which all-cause mortality exponentially rises for all successive age brackets.

Aging can thus be viewed as the general deterioration in human health over the life span generally associated with development of debilitating and life-threatening disease processes. Indeed, aging has been defined as the spectrum of changes that render human beings progressively more likely to die (Medawar, 1952). As shown in **FIGURE 1.7**, the prevalence of major chronic diseases (arthritis, heart disease, cancer, diabetes mellitus type 2, and chronic obstructive pulmonary disease) rises exponentially with age. It is obvious that the phenotype of human aging is one in which practically any system, tissue, or organ can fail, resulting in debilitation and death (Austad, 1997; MacNee, Rabinovich, & Choudhury, 2014; Strehler, 1999). Nevertheless, it is important to stress that aging is not merely a collection of diseases. Rather, certain pathologic conditions progress in parallel with the aging process while others, such as asthma, remain constant or even decline late in life.

Aging of Human Cell Populations

Aging is a complex and controversial subject. The aging phenomenon appears to be driven by deterioration in cellular health. The human body consists of tens of trillions of cells. This huge population of cells is divisible into subpopulations, each consisting of billions of cells that comprise certain anatomic structures, organs, and tissues. These component cell populations exist in a state of relative homeostasis performing the essential functions of life.

Studies of aging suggest that different cellular populations comprising the human body of a single individual do not all age at the same rate. Acceleration of the aging phenomenon in even one critical cell population may create a "weak link" for the entire system resulting in debilitation and death. However, as pointed out by Hayflick, the aging process does not share its elemental features with any particular disease

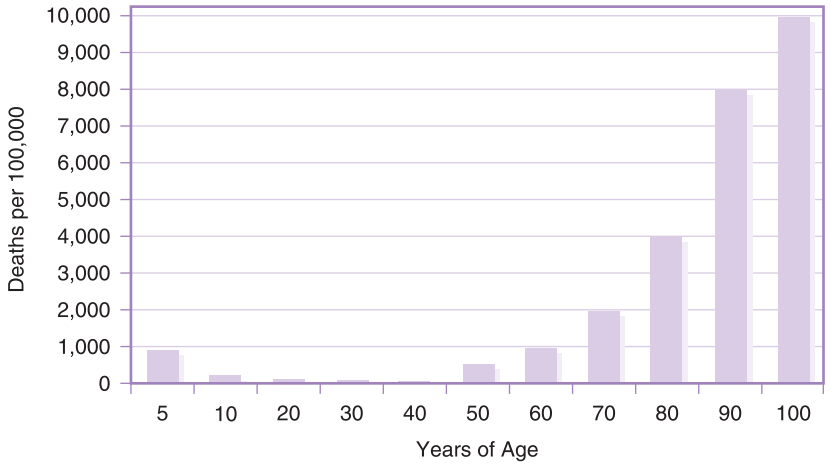


FIGURE 1.6 Characteristic Death Curve Modeled on the U.S. Population 2002.

Data from Aris, E. (2004). United States life tables, 2002. *National Vital Statistics Reports, 53*(6), 1–40.

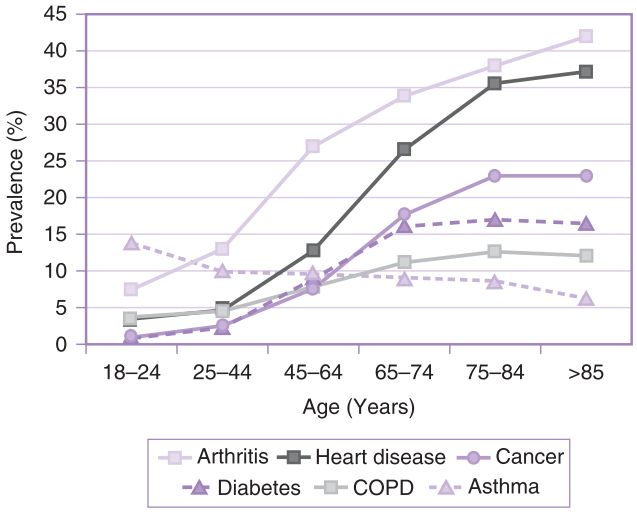


FIGURE 1.7 Prevalence of Selected Chronic Conditions Expressed as Percentages, as a Function of Age for the U.S. Population (2002–2003 Dataset).

Data from National Center for Health Statistics, Data Warehouse on Trends in Health and Aging, 2003.

(Hayflick, 2007). This observation led him to state that, "*the fundamental aging process is not a disease but it increases vulnerability to disease*." To paraphrase, aging may be the cause but not necessarily the effect of a disease process.

The preservation of homeostasis among populations of normally functioning cells in the human body depends primarily upon the balance of cell death and cell replacement. If cells die faster than they are replaced, then the progressively greater demands placed upon those cells that remain may eventually lead to pathologic changes and rapid deterioration in cellular health. Any one of multiple intrinsic and extrinsic factors capable of upsetting the balance of cell death and cell replacement may therefore have considerable impact on the aging phenomenon, particularly for those cell populations that do not normally undergo cell division (e.g., neurons and mature muscle cells).

Programmed cell death (called apoptosis) and cell division are tightly regulated by genetic factors; nevertheless, both processes are also subject to modulation by extracellular as well as intracellular molecular factors. Aging may thus result from extrinsic or intrinsic factors that cause an accumulation of cellular and tissue damage, or alternatively, changes in gene expression related to DNA damage and somatic mutations, epigenetic factors such as methylation or acetylation of DNA, or structural modification of DNA by the intrinsic biological clock that regulates the number of cell divisions (e.g., telomere shortening in chromosomes) (Campisi, Kim, Lim, & Rubio, 2001). The etiology of the aging phenomenon therefore appears similar to most complex human traits. Aging is influenced by genetic and environmental factors that interact to produce significant phenotypic variability. Two key theories of aging are briefly discussed in the following sections: one involves the energy rich microenvironment of the cell and the other the genetically controlled biological clock of cell division.

Free Radical Theory of Aging

More than half a century ago, Denham Harman developed the free radical theory of aging (Harman, 1956). His theory states that aging is a consequence of accumulating oxidative damage to cells and cellular components over time (reviewed in Beckman & Ames, 1998). Harman later extended his theory to include mitochondrial production of free radicals during normal cellular respiration (Harman, 1972).

Free radicals and oxidants, commonly called reactive oxygen species (ROS), are highly unstable

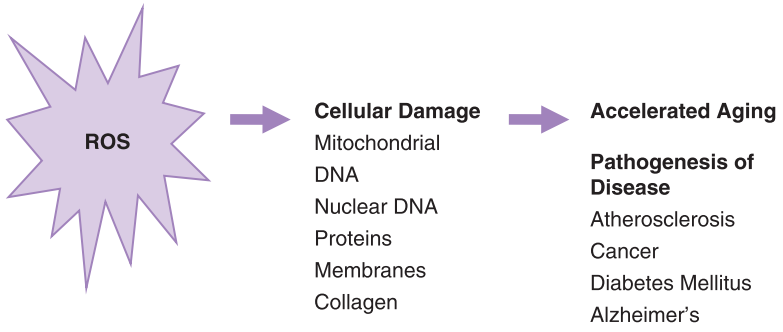


FIGURE 1.8 Free Radical Theory of Cell Damage, Aging, and Chronic Disease.

reactive molecules that can damage many vital cellular components (**FIGURE 1.8**). Rebecca Gerschman and colleagues discovered that ROS can originate from exogenous sources such as ultraviolet and ionizing radiation and were the first to suggest that free radicals are toxic agents (Gerschman, Gilbert, Nye, Dwyer, & Fenn, 1954).

ROS can be formed by exogenous processes such as irradiation and inflammation as well as normal cell metabolism. These short-lived molecules include superoxide, peroxide, hydroxyl radicals, and reactive nitrogen species such as peroxynitrite, all of which are unstable and readily react with DNA to cause a variety of structural genetic alterations including base pair mutations, rearrangements, deletions, insertions, and DNA sequence amplification. While DNA mutations, alterations, and chromosomal abnormalities increase with age in mice and other laboratory animals, damage to nuclear diploid DNA by ROS remains an unproven cause of aging (Ames, Shigenaga, & Hagen, 1993).

Oxidative phosphorylation is responsible for energy production within the mitochondria of virtually all cells. Since this process continually produces ROS such as superoxide and hydrogen peroxide, and since mitochondria possess haploid DNA unprotected by histones, many advocates of the free radical theory of aging consider that oxidative damage to mitochondria and the mitochondrial DNA has a primary role in the aging process (Barja & Herrero, 2000; de Grey, 1997; Harman, 1972; Linnane, Marzuki, Ozawa, & Tanaka, 1989).

Certain nutraceutical agents have gained favor as free radical scavengers that offer some protection against oxidation and the formation of ROS. These include ascorbic acid (vitamin C), tocopherol (vitamin E), carotenes, melatonin, and antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase that are capable of degrading ROS into inert compounds (Ames, Cathcart, Schwiers, & Hochstein, 1981).

Telomere Shortening and Aging

Cell division is an extraordinarily precise process that gives rise to daughter cells that have *almost* exactly the same genetic constitution as their progenitors. However, with every cell division, there is incomplete duplication of the chromosomal tips (called telomeres). Successive cell divisions therefore result in shortening of chromosomes until a point is reached where the daughter cells are no longer capable of dividing (called the "*Hayflick Limit*" after its discoverer). Since cells that reach their Hayflick Limit cannot replicate, the balance of cell replication and cell death is interrupted and cellular health may deteriorate. This is the basis of the *Telomere Theory of Aging*; namely, as an ever-increasing percentage of cells reach their Hayflick Limit and are unable to reproduce, then defense, maintenance, and repair of the body becomes increasingly impaired. Thus, telomere attrition due to the Hayflick Limit could account for most of the decline in functional efficiency of cell populations and increases in vulnerability to chronic diseases that characterize the aging phenomenon (de Magalhaes & Faragher, 2008; Hayflick, 1985, 2007).

Declining Fertility Rate in Women

Over the past half century, the worldwide fertility rate (the average number of births per woman during the childbearing years) has been cut in half, from 5.0 in the 1950s to 2.5 in the 21st century (**FIGURE 1.9**). The decline in fertility rates has been sharpest in the most populous nations such as China, India, and Russia. For example, the fertility rate in China, which has the world's largest population (1.38 billion), decreased from more than 6 in 1970 to 1.6 births per woman in 2017, well below the worldwide