Physiological Basis of Aging and Geriatrics
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Fourth Edition

Edited by
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The publication of the fourth edition of *Physiological Basis of Aging and Geriatrics* comes at a particularly opportune time. The lengthening of life expectancy at birth and in old age, which began in the twentieth century, has reached both industrialized and, increasingly, developing countries. Currently, individuals aged 80 years and older appear to be the fastest growing segment of the human population, and centenarians, once rarely seen, are much more frequently encountered. Understandably, these demographic changes are being accompanied by a new way of thinking about aging.

In the early twentieth century, the study of aging focused primarily on biomedical models of pathology, that is, how to diagnose the diseases and chronic disabilities afflicting the elderly, and how best to treat them. It is safe to say that most scientists studying aging before the 1980s regarded aging as a rising wall of mortality. Since then, however, due to a multiplicity of factors, social as well as medical, we have witnessed a major effort among researchers to reinterpret aging as a normal, healthy, and even positive feature of the life span. Although aging may make older adults more susceptible to disease, most retain sufficient plasticity and regenerative capability to ensure functional competence, which may determine how successfully, if not how long, aging populations may live. As we now view them, aging and death, much like development and maturation, entail numerous, complex interactions that have encouraged researchers to turn their attention to the physiological basis of aging as well as the genetic and environmental factors that alternately enhance and impair functional competence at molecular, cellular, and organismic levels.

Chapters are grouped into three main parts: In Part I, *General Perspectives*, aging is viewed as an individual’s “journey taking place in a community setting.” It describes the demographic, epidemiologic, and comparative aspects of aging and discusses molecular and cellular aspects of aging in relation to several theories of aging, thus providing a comprehensive profile of aging in individuals and populations. Part II, *Systemic and Organismic Aging*, surveys the aging of body systems, focusing on maintenance of optimal functioning and adaptation to environmental demands. Part III, *Prevention and Rehabilitation*, presents a synopsis of pharmacologic, nutritional, regenerative, and assistive interventions that promote successful aging and longevity. Using physiology as its unifying concept, the fourth edition contains concise, explicit explanations and numerous comprehensive tables and graphs. Clinical correlations are included as a practical reference for the geriatrician and as a guide to normal aging for the gerontologist.

Comparable books on aging target a professional and/or academic readership; here, the goal is to offer information that will be useful to a broad spectrum of readers from different biological and educational backgrounds. We believe it will not only meet the needs of those preparing for a career in gerontology or geriatrics or interested in aging as a specific topic in biological sciences, but also of older persons themselves, along with their families and caretakers, who seek to better understand the aging-related changes and to gain new insights about this stage of life.

When the elderly are viewed through the eye of the clinician, the emphasis is on the need for assessing, managing, and reducing risk factors. Equally important, as we begin to see aging in a new light, is strengthening physiologic competence and devising appropriate interventions aimed at improving quality-of-life. The concept of “continuity through change” is fundamental to all biological processes. As individuals and society itself age, continuity of prior events may provide “a usable past” that can serve us well in shaping future functions. Indeed, in a 1972 book, *Developmental Physiology and Aging*, (Timiras) identity was shown to be as dynamic a process among the elderly as it is in the young. Slowing or otherwise mitigating the effects of old age by strengthening physiological competence throughout life does not deny the inevitability of death, but it does deny the inevitability of disability, disease, and despair. In this first quarter of a new century, we have every reason to rejoice in the vigorous declaration of the nineteenth century English poet, Robert Browning’s, “Grow old along with me/The best is yet to be/The last of life for which the first was made/Grow old nor be afraid!”

Paola S. Timiras
I have been greatly encouraged in preparing this fourth edition by the participation of several of the collaborators of the first, second, and third editions and by the equal enthusiasm and expertise of the first-time co-authors. All have willingly accepted the task of reviewing, updating, or preparing anew their respective chapters or sections within stringent deadlines. To them, I offer my most heartfelt thanks for an extraordinarily well-accomplished performance.

Special thanks to Dr. S. Oklund for the many drawings, which effectively illustrate and integrate the complex material presented.

I also wish to thank my assistants, Irene Thung and Brian Bui, who competently prepared the manuscripts according to the specifications of the publisher and dealt with the word processing, editing, and formulation of the many tables that effectively integrate the diverse information.

I thank the editing team of Informa Healthcare and The Egerton Group for their vigilance about the progress of the book and its many drafts. In particular, I would like to thank Sherri Niziolek, Sandra Beberman, Chris DiBiase, and Ginny Faber.

Finally, I would like to recognize the silent encouragement of the many hundreds of students who have taken, over the years, my class, “Physiology of the Aging Process.” By their enrollment in the class, interest in the subject matter, their criticism or praise, they have inspired me to continually improve, streamline, and update the course material, a process which has resulted in the subsequent editions of this book.
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Part I

General Perspectives

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Old Age as a Stage of Life: Common Terms Related to Aging and Methods Used to Study Aging

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THE “LONGEVITY REVOLUTION” AND ITS IMPLICATIONS

Perhaps two of the greatest human achievements to have occurred from prehistoric to more recent times, and, particularly, in the last two centuries, are the increase in the human population worldwide and the extension of human longevity. Thanks to improved living conditions stemming from advances in agricultural practices and advances in industry and technology, the human population today has reached an unprecedented size (1–3). Living conditions have greatly improved due to

1. public health reforms and improved personal hygiene,
2. advances in medical knowledge and practices,
3. vastly increased control over the environment, and
4. rising income and standards of living.

Never in human history have so many humans lived longer: In the United States, for example, the percentage of Americans aged 65 and older, relative to the entire U.S. population, rose from 4% in 1900 to 8% in 1950 and to 13% in 1990, and these increases are even greater in the population statistics of other countries (Chapter 2). Indeed, because of this longevity revolution that owes much to improvements in technology and extraordinary advances in biomedicine, industrialized countries are now faced with a large graying population; individuals in the “healthiest” countries now have a life expectancy at birth of 80 years and longer (Chapter 2).

Although it is difficult to predict with certainty what will happen in the future, it is expected that this trend toward increased longevity will continue, at least in the most developed countries. For example, it is predicted that by the year 2030, about one-fifth (18%) of the population of the United States will live to 65 years and longer (4,5).

Today, in several developed countries, the rise in the proportion of the elderly relative to the total population is associated with a decline in the proportion of young people (Chapter 2). This phenomenon has to do not only with the increased longevity of the elderly, but also with the decrease in the number of the young persons. Despite a reduction in infant mortality worldwide, attributable to successful preventive public health and medical interventions, we have seen a concomitant reduction in fertility, which has been attributed to various socioeconomic and lifestyle factors. For example, in Italy, the average number of births in the family has fallen from 4.67 in 1850 to 3.14 in 1900, to 1.88 in 1950, and to 1.3 in 2005 (6,7). To adjust to a population shift where the elderly represent a predominant group, societies must rearrange their economic, technologic, medical, and educational priorities. Such adjustments are as costly as they are difficult to accomplish, for while both younger and older persons have a similar degree of vulnerability, their needs are quite different. Thus any change in priorities must be based on a solid understanding of the fundamental principles that regulate human aging if we are to achieve optimal social, economic, and medical support for both groups.

In regard to older persons, such planning necessarily involves (i) repudiating persistent myths and stereotypes of old age (Box 1) and replacing them with a firm grounding in what we now know about the physiology of human aging, and (ii) adopting new guidelines compatible with recent demographic changes (Box 2) and incorporating a realistic view of current and future physiotechnological advances. According to the renowned economist Fogel, “health care is the growth industry of the twenty-first century. It will promote economic growth through its demand for high-tech products, skilled personnel, and new technologies” (2).

SIGNIFICANCE OF PHYSIOLOGY IN HUMAN AGING

Why focus on the physiology of human aging rather than on the diseases of old age? Until recently, pathologic processes in old age were studied extensively with the intent of combating diseases specific to this high-risk group; the physiology of aging was not of primary interest. Understandably, it is difficult to isolate “normal function” (the domain of physiology) from “abnormal function” (the domain of pathology); aging, while resulting from a “normal” process, nevertheless leaves us increasingly vulnerable to degenerative diseases.

In these early years of the twenty-first century, however, aging is being regarded anew as a positive and potentially rewarding process, free of the stigma it has had in the past of inevitable decline in health and productivity. With the introduction of the concepts of “successful” or “healthy” aging, many researchers are shifting attention from a primary focus on the diseases of old age to the possibility of strengthening normal functional competence at the molecular, cellular, and organ systems levels over the life span (8–10). During the life span, according to Hayflick, “the level of physiologic capacity reached at the age of reproductive success in living things is taken as the determinant of their potential longevity” (11). While aging is not a disease, it may result from increasing “molecular disorder” in the cells of vital organs (11). The simplistic and hotly disputed statement that “aging is cell aging” links the reduction in or loss of the compensatory and regenerative functional capacity of cells and organs with aging to an increase in susceptibility to disease and death (12) (Chapter 4).

One of the many problems encountered by those who study aging is that, thus far, aging has defied all attempts to...
establish objective landmarks, as menarche, does at puberty. Old age in humans is conventionally accepted as the stage in the life cycle that begins at around 65 years of age and terminates with death. However, given the considerable heterogeneity of the elderly population and the complexity of physiological processes, it is difficult to circumscribe the physiologic boundaries of aging in temporal terms. Rather, the onset of aging occurs at some indeterminate point in the mature individual and its progression follows timetables that differ with each person and vary depending on genetic and environmental factors.

Indeed, “physiologic heterogeneity” is one of the consistent characteristics of the elderly population (Chapter 3).

**ORGANIZATION OF THE CHAPTERS**

This book comprises 25 chapters divided into three parts: **General Perspectives**, **Aging of Systems and Organs**, and **Prevention and Rehabilitation**. Our goal is to provide a book that will be useful to a broad spectrum of readers: those preparing for a career in gerontology or geriatrics, those interested in aging as a specific topic in biology, and older persons (as well as their families and caretakers) who would like to better understand and distinguish age-related changes occurring in the body over time. The joint fields of gerontology and geriatrics are fast expanding, and they attract people from many disciplines, all of whom require a common understanding of the fundamental principles of aging. Using physiology as the unifying concept, this book assimilates and distills information from multiple sources to produce a comprehensive text accessible to a wide audience.

Any consideration of the aging process cannot ignore psychological, social, and economic components, and this is particularly so for the geriatrician, who must deal with the patient from a holistic perspective. Although such factors are vital to a full understanding of this phase of life, an in-depth exploration of their contribution is beyond the scope of this book; the reader will be referred to appropriate publications for further study.

**THE JOURNEY OF LIFE**

Historically, chronological age has been used to assess the transition from one stage of life to the next. In its broadest sense, the human life span can be divided into two main periods:
Like in times past, people turning 50 today have nearly half of their adult life ahead of them. While the quality of their physical life will be considerably better than that of their predecessors, what about their social, political, and economic life that is so vital to well-being? And when they retire, will they opt for a lifestyle of leisure and recreation or will they choose to continue working or volunteering their skills? And, for the less fortunate elderly, what will be the choices they can afford? Responding to these questions is a critical task not only for individual men and women in this age group, but for society worldwide (7–9). As communities across the United States and other nations continue to develop policies and services for their citizens, it becomes increasingly important, given today’s demographic realities, that thought be given to society’s older members. As in all planning efforts in this area, establishing a sound policy starts with needs surveys by age group, by gender, and, for the elderly, by health status. Determining the level of health among older members allows each community to evaluate the potential of this age group to continue contributing to society. Beyond the services typically provided for “seniors”—low-cost clinics, community centers, assistance with taxes and such—policy makers may broaden their vision, finding ways to

- strengthen public health education to include recommendations about hygiene, nutrition, and physical exercise in this population, and
- create opportunities for the elderly to participate more actively in the community (e.g., working part-time on a paid or volunteer basis in outreach programs, in service jobs, as mentors, and as school resource volunteers) not simply to enhance their own lives but to procure vital services that benefit the community at large.

Indeed, if not struggling with disease or poverty, the elderly represent individuals who are variously skilled, literate, energetic, and well informed. Their survival alone suggests a certain resilience. It is well known among educators that holding low expectations is not conducive to achievement. Yet, do we not hold low expectations of the elderly when we bow down to the myths of aging and arbitrarily reject them as contributing members of society, as buoyed by a sense of purpose and meaning as their counterparts in youth and adulthood? At the societal level, it is foolhardy, in fact, to regard older adults as a “throw-away” population whose usefulness is at an end when, in reality, they represent a largely untapped resource, particularly in the United States (7,8). It follows, then, that if society is to benefit from the contributions of older people, the agencies and programs set up to provide them with services and programs would do well to

- re-educate themselves about the realities of physiologic aging,
- view retirement as a lifestyle transition, not a termination of employment,
- maintain high expectations of senior citizens, and, of course,
- distinguish between those in need and those able and willing to serve the needs of others.

Few in this age group need or want to take to their rockers; it is well documented that pursuing useful activities enables older adults to stay physically and mentally alert, flexible, and in touch (9) (Chapter 7).

Leo Tolstoy in the nineteenth century went beyond that limited prescription when he wrote in a letter to a friend, “Don’t complain about old age. How much good it has brought me that was unexpected and beautiful... [and] the end of old age and of life will be just as unexpectedly beautiful.”


preadental and postnatal (Table 1). In contemporary Western society, the postnatal period is identified by a chronological timetable that states: “children begin school at age five, young people go to work or to college at 18, old people retire at 60 or 65... Age is being taken as a criterion for sequencing the multiple roles and responsibilities that individuals assume over a lifetime” (13). In terms of physiology, the most striking changes take place in the embryonal and fetal stages when the developing organism is most “plastic,” that is, most susceptible to being modified or modulated by external (e.g., nutrition, physical exercise) and internal (e.g., hormones) influences. Compensatory and regenerative changes continue to occur even in adulthood and old age, although, given their slower pace, these changes do not produce results on a par with those possible at younger ages.

Many animal species are capable of an independent existence at relatively immature ages; other species, including the human species, are not. The human newborn is utterly dependent on adults for food and care. Additionally, throughout infancy, childhood, and adolescence, remodeling of body shape continues gradually, together with the acquisition of new functions and the improvement of those already established. The need for nurture of the immature human infant, child, and adolescent has led to the formulation of an evolutionary explanation for the increased life span of the parents and grandparents; that is, even though the older generations either have lost or have experienced diminished capacity to reproduce, they have played, and continue to play an essential role in the preservation of the species by raising and protecting young humans until they have reached maturity and self-support (14). Developmental changes are complete at about 25 years of age, and the body is stabilized in its adult condition. The mature adult period lasts for approximately another 40 years and encompasses the period of maximal physiologic competence.
As indicated previously, the span from 65 years until death was viewed in the past as a period of progressive decline in normal function and of inevitable increase in disease and disability. The substantial heterogeneity among old persons and observations of positive trajectories of aging without disease, disability, and major physiologic decline have offered a more positive model of successful or healthy aging (Chapter 3). Accordingly, while some of the pathologic processes that may accompany aging will be discussed, in general, the focus throughout this book is an optimistic one for this population.

## Prenatal and Early Postnatal Life Stages

Both prenatal and postnatal stages may be subdivided into several periods, each distinguished by morphologic, physiologic, biochemical, and psychological features. The main divisions and the approximate time periods of the life span in humans are listed in Table 1.

The prenatal period encompasses three main stages: ovum, embryonal, and fetal. The postnatal period begins with birth and continues into neonatal life, infancy, childhood, adolescence, adulthood, and old age. The concept that the life span is divisible into successive stages is not new. Those writing in antiquity established three, four, and seven periods of life for mankind (15). For example, Aristotle divided life into three ages: growth, stasis, and decline. This was modified later in Greek medicine and physiology into four age periods: childhood, youth, maturity, and old age.

While it is necessary in practical terms for researchers to fragment the biologic study of living organisms, such divisions can obscure the dynamic relationships that operate at many levels of organization and cross artificially set age boundaries. We should recall here that human development depends on “a program of genetic switches that turn on in a highly regulated manner, at specific places (in the organism) and times,” and that “responses to environmental challenges fostering changes early on may reverberate decades later in the guise of cardiovascular diseases and diabetes” (16). Indeed, there is increasing experimental and epidemiological evidence suggesting that events in earlier ages (and even in utero) can set the stage for disease in adult and old ages (5,16,17) (Chapter 3). Thus the physiologic profile of a given individual must be assessed with regard to his or her particular life history in all its biosocial complexity. As has been said, “growing old gracefully is the work of a lifetime!”

### Stages of Maturity and Old Age

The mature years are considered a major life stage characterized by stability as manifested in optimal and integrated function of all body systems. Indeed, function in adulthood is taken as a standard against which to measure any degree of physiologic or pathologic deviation that may have occurred at younger ages or becomes apparent with age. In most textbooks of human physiology, the mature 25-year-old, 70 kg, 170 cm male is taken as a point of reference. However, because functional competence is multifaceted, and optimal performance may differ from age to age and from one functional parameter to another, it would be physiologically incorrect to assume that a function is maximally efficient only during adulthood and that differences in one’s earlier or later years necessarily represent functional immaturity or deterioration, respectively. Rather, physiologic competence must be viewed as having several levels of integration, depending on the requirements of the organism at any specific age and the type and severity of the challenges to which the organism is exposed. Indeed, adequate function of several selected organs and systems may persist into old age.

**Physiology represents the study of function at all levels of biological organization.** For this reason, the techniques used by physiologists are often borrowed from other disciplines. Nevertheless, there are certain techniques that are used repeatedly in gerontological studies. **Cross-sectional and longitudinal methods** represent some of the most frequently applied in studies involving humans. Measurements such as activities of daily living (ADL) and instrumental activities of daily living (IADL) continue to be used to assess physiologic competence and the presence or absence of disease and disability (Chapter 3).

Some of the major difficulties encountered in studying aging in any organism at any specific age is the type and severity of the challenges or stress factors to which the organism is exposed (Chapter 9). In several organs and systems, adequate function often persists into old age. Although the age of 65 years has been accepted as the demarcation between maturity and old age, a person of that age may be quite healthy and a long way from “retiring” from the workplace or, more generally, from the demands of daily life.

If it is difficult to subdivide the adult years into physiologic stages, old age presents even more of a challenge in this regard (Chapter 3). In the elderly, it can be said that:

- There is great heterogeneity of responses among individuals of equal age.
- Changes do not involve all functions to the same degree and at the same time.
- The timetable of functional changes is differentially susceptible to specific intrinsic and extrinsic factors (Chapter 3).

### Death vs. Immortality

While old age is approached gradually, without any specific physiologic markers of its onset, death is the terminal event that ends life. In broad terms, causes of death may be classified as trauma, accidents, and disease (Chapters 2 and 3). Trauma and accidents (e.g., high-speed vehicle crashes, dangerous occupations, drug abuse, cigarette smoking) are the major causes of

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**TABLE 1  Stages of the Life Span**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal life</td>
<td>Fertilization through week 1</td>
</tr>
<tr>
<td>Ovum</td>
<td>2–8 wk</td>
</tr>
<tr>
<td>Embryo</td>
<td>3–10 mo</td>
</tr>
<tr>
<td>Fetus</td>
<td></td>
</tr>
<tr>
<td>Birth</td>
<td></td>
</tr>
<tr>
<td>Postnatal life</td>
<td></td>
</tr>
<tr>
<td>Neonatal period</td>
<td>Newborn; birth through week 2</td>
</tr>
<tr>
<td>Infancy</td>
<td>Week 3 until end of first year</td>
</tr>
<tr>
<td>Childhood</td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>2–6 yrs</td>
</tr>
<tr>
<td>Middle</td>
<td>7–10 yrs</td>
</tr>
<tr>
<td>Later</td>
<td>Prepubertal; females ages 9–15; males 12–16</td>
</tr>
<tr>
<td>Adolescence</td>
<td>The 6 yrs following puberty</td>
</tr>
<tr>
<td>Adulthood</td>
<td>Between 20 and 65 yrs</td>
</tr>
<tr>
<td>Senescence</td>
<td>From 65 yrs to death</td>
</tr>
<tr>
<td></td>
<td>65–74—young-old</td>
</tr>
<tr>
<td></td>
<td>75–84—old-old</td>
</tr>
<tr>
<td></td>
<td>85+—oldest-old</td>
</tr>
<tr>
<td>Death</td>
<td></td>
</tr>
</tbody>
</table>
death in young adulthood. Cancer, cardiovascular diseases, and metabolic diseases are the most frequent causes of death in older adults (Chapter 3). Death need not be related exclusively to aging; disease processes that overwhelm the body’s defense or repair mechanisms affect persons of all ages, but they are particularly life endangering in the very young and in the very old.

Many diseases, primarily infectious ones, that lead to death in the perinatal and childhood periods—periods of high risk—have been conquered in developed countries. In the United States, the majority of deaths from disease occur in the elderly in whom diminished function makes the accumulation of pathologic events less tolerable than in the young. Indeed, some diseases (e.g., degenerative diseases) occur almost exclusively in the old, and this linkage of pathology with old age has been invoked by some investigators to support the argument, ardently denied by others, that aging itself is a disease. However, old age is not an accepted natural cause of death and is not reported on the death certificate. Although there may be differences of opinion about how long humans might live, there has never been any doubt about the inevitability of death.

The tacit acceptance of a debilitating old age is now being replaced by one that regards senescence as the “subversion of function,” the inevitability of which is open to question. The question now being raised is whether it is simply a “design fault” that we age and die (18,19). Organ or cell transplantation, or cloning, i.e., replacement of defective organs or cells with better functioning ones, represent somewhat clumsy ways to postpone death. Research exploring new pharmacologic, genetic, and bioengineering technologies as well as on improving nutrition and lifestyle habits offers startling potential for ameliorating and prolonging life (Chapters 22–25).

With the elucidation of the human genome, genetic research is attracting increasing support because of its potential use in diagnosing and treating disease. Until now, humankind has considered immortality in the light of extending our life through our offspring; genes, in a sense, are immortal. For many, however, this sense of immortality no longer seems adequate. They are frustrated that in a time when humans have gone into and returned from outer space and manipulated DNA, they have not conquered death. Death, indeed, remains the last “sacred” enemy to be conquered.

The concept of a single causative factor to account for aging pervades many areas of biologic study, and gerontology is no exception. However, it is unlikely that a single “triggering” event is responsible for the aging and death of the human organism; rather, aging and death probably entail numerous and complex interactions at different genetic and environmental levels (18–22). The fact that we cannot answer many questions at this time and that the nature of the aging process remains unclear, need not deter our search. Only by continually posing bold new questions can we hope to accomplish the spirited goals of gerontologists: to “add years to life and life to years.” Biologists working in the area of aging have defined three major goals:

1. To prolong human life
2. To significantly enhance physical vigor and vitality at all ages
3. To prevent or treat diseases throughout the life span

New research allows a glimpse into a world in which aging and, perhaps, even death due to age-related diseases, may at least be delayed considerably (19).

### COMMON TERMS RELATED TO AGING

The interpretation of aging as a physiologic process upon which pathology and disease are superimposed has been formalized under the separate disciplines of gerontology (the study of aging processes) and geriatrics (the prevention and treatment of the disabilities and diseases associated with old age) (Table 2). The terms “aging,” “old age,” and “senescence” are often used interchangeably despite some substantive differences. “Aging” refers more appropriately to the process of growing old, regardless of chronologic age; for our purposes here, it includes all the physiologic changes that occur with the passage of time, from fertilization of the ovum to death of the individual. The World Health Organization breaks down “old age,” classifying persons 60 to 74 years of age as the young-old, those 75 to 84 as the old-old, and those 85 years and older as the oldest-old. Centenarians, of course, are individuals 100 years old and older (Table 2). “Senescence” is generally restricted to the stage of old age characteristic of the later years of the life span (Table 2).

### TABLE 2  Brief Glossary of Aging-Related Terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aging</td>
<td>Latin “aetas.” The lifelong process of growing older at cellular, organ, or whole-body level throughout the life span</td>
</tr>
<tr>
<td>Geriatrics</td>
<td>Greek “geron,” old man, and “iatros,” healer. The branch of medicine specializing in the health and illnesses of old age and the appropriate care and services</td>
</tr>
<tr>
<td>Gerontology</td>
<td>Greek “geron,” old man, and “logos,” knowledge. The multidisciplinary study of all aspects of aging, including health, biological, sociological, psychological, economic, behavioral, and environmental factors</td>
</tr>
<tr>
<td>Senescence</td>
<td>Latin “senex,” old man. The condition of growing, limited to old years</td>
</tr>
<tr>
<td>Life span</td>
<td>The duration of the life of an individual/organism in a particular environment and/or under specific circumstances</td>
</tr>
<tr>
<td>Average life span</td>
<td>The average of individual life spans for members of a group (cohort) of the same birth date</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>The average amount of time of life remaining for a population whose members all have the same birth date and based on a given set of age specific death rates (generally the mortality conditions existing in the period mentioned)</td>
</tr>
<tr>
<td>Active life expectancy</td>
<td>As above, with the additional idea that the years of life be free of a special level of disability</td>
</tr>
<tr>
<td>Longevity</td>
<td>Long duration of an individual’s life; the condition of being “long-lived,” also often used as a synonym for life span</td>
</tr>
<tr>
<td>Maximum life span</td>
<td>The length of life of the longest-lived individual member of a species</td>
</tr>
<tr>
<td>Biomarkers</td>
<td>Physiologic and anthropomorphic measures (morphological, functional, and behavioral) specific to old age</td>
</tr>
<tr>
<td>Physiology</td>
<td>The science that treats the functions and activities of the living organism and its parts</td>
</tr>
<tr>
<td>Pathology</td>
<td>The science that deals with the nature of disease (of molecular, cellular, tissue, and organ systems)</td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>The quality of being composed or consisting of dissimilar elements or ingredients; with respect to human population, the diversity of function within a specific age group from the molecular to the systemic level</td>
</tr>
<tr>
<td>Plasticity</td>
<td>The capacity to be modified or molded by hereditary and environmental influences</td>
</tr>
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Source: Adapted, in part, from Ref. 23.
METHODS USED TO STUDY AGING

Human Studies

Physiology represents the study of function at all levels of biological organization. For this reason, methods and protocols to study aging in humans are difficult to implement. Therefore, the use of animals or of tissues/cells in vivo or in vitro often are substituted in place of human studies.

Some of the major difficulties encountered in studying aging in humans include:

- The heterogeneity of the aging process in individuals as well as in the total number of individuals in a population
- The heterogeneity of the aging process in systems, organs, cells, and molecules of a single individual
- The considerable duration of the human life span that makes it extremely difficult for one investigator or group of investigators to follow functional changes in the same individual or individuals from conception to death
- The limitation of experimental intervention in humans due to ethical considerations
- The differential influence of genetic and environmental factors in individuals of different age, race, ethnicity, and sex, as well as socioeconomic, health, disease, and disability status.

Animal Studies

Animal studies are often chosen by researchers because of availability, cost, ease of maintenance, and popularity with funding agencies, even though they may not be the best choice for the research in question (22,24,25). Criteria that are important to consider in choosing an animal model are species, sex, genetic properties, and research goals. These criteria must embody the following characteristics:

- Specificity: The model must exhibit the trait (e.g., function) of interest.
- Generality or transferability: The results observed in the chosen model must be applicable to other species.
- Feasibility: The availability, cost, and convenience of the model must be reasonable.

To investigate the applicability of a given study of the aging process and longevity in animals to humans, a number of successful approaches have relied on the use of flies and worms. The costs involved are low, and these invertebrates are readily available, live a short life, and require little space (Chapters 3 and 4). For example, large-scale studies of medflies (Ceratitis capitata) have provided an extensive database of longevity and age- and sex-specific mortality for millions of these flies from the early 1990s to the present time (25). In another species of fly, Drosophila melanogaster, it was found that physiological performance at later ages and resistance to stress could be extended by selective breeding of the oldest animals in the colony; with the increased longevity, these flies exhibited a higher level of reproduction at later ages but at the cost of reduced fecundity in early life (26,27). In some worms (Caenorhabditis elegans), the life span can be increased by as much as six times in some mutants by suppressing the common receptor for the hormones, insulin/insulin-like growth factor (28). In worms, as in flies, while resistance to stress is increased, growth and reproductive functions are reduced (29) (Chapter 3).

Most organisms, from yeast to mammals, suspend reproduction during periods unfavorable for reproduction by entering a different physiologic mode. For example, when food is scarce, yeast enters, a stationary phase during which reproductive activities are interrupted (30,31). Similarly, medflies may change from "waiting" to "reproductive" mode when they improve their diet, from sugar-only to full-protein. In yeast, as well as in worms and flies, an increase in the activity of sirtuins, enzymes associated with life span control, increases longevity. The opposite effect is observed when the sirtuin enzyme is either diluted or reduced; in yeast, the life span shortens by as much as 30%. Sirtuins (e.g., SIRT1) are found in humans, and, although there is reason to suspect that they play a role in the aging of human cells as well, definitive evidence remains to be established.

Another currently popular approach uses mostly mice to create a unique animal model (Chapter 4). With the advent of recombinant DNA technology and the ability to genetically engineer new animals, investigators are now able to alter a specific gene or process. The resulting transgenic animals, the most frequently used being transgenic mice, carry a fragment of foreign DNA integrated in their genome or have a portion of the genome deleted or mutated (32). In this manner, the role of individual genes may be studied in normal function (as in functional genomics) and in diseases, and potential genetic effects on aging may be clarified (Chapter 4).

Still another approach to the experimental study of the aging process uses single cells or fragments of tissues removed from the body and cultured under in vitro conditions. Such studies establish standardized conditions of cell culture for cells and tissues derived from individuals of different chronological ages and compare specific parameters of cell function such as replication and metabolism. For example, "cell doubling capacity" is taken as one index among several of cell reproductive capability (33) (Chapter 4). Cultured cells and tissues may serve as models for identifying specific cell functions or mimicking aging pathologies characterized by specific types of cell aging. In addition, cells from different tissues, made to de-differentiate in culture, may then be trans-differentiated into cell types of different tissues (34).

Examples of the ways in which comparative studies in animals allow us to better understand aging processes in humans are presented throughout this book.

HEREDITARY AND ENVIRONMENTAL INFLUENCES ON AGING

Developmental processes and their regulation by heredity and the environment have engaged the attention of biologists for many decades. The completion of the Human Genome Project has opened a new and exciting era of studies to identify genes responsible for turning on and off those switches that regulate the ability to adapt to the environment and the length and quality of life. Gene mutants for lengthening or shortening the life span have now been identified in a number of animal species (Chapter 4). While genes dictate the composition of a cell or organism, they also may predispose adult and elderly individuals to a number of complex pathologies caused by environmental risk factors. However, environmental influences may modify both genetic physiologic and pathologic characteristics: the term phenotype (or phenoype) represents the observable properties that an organism has developed under the combined influences of its genetic constitution and the environmental factors to which it has been exposed. Thus the genes/environment hypothesis of aging states: “the genome proposes but the phenotype disposes” (35). At all stages of life, the directing force of heredity and the modifying influences of the
internal and external environment unite in determining physiologic competence and length of the life span (Fig. 1). Heredity operates through internal factors present in the fertilized egg. The genes, or hereditary determiners located in the chromosomes, contain the genetic contribution of each parent. Indeed, it has been said that “the best assurance for a long life remains the thoughtful selection of long-lived parents.” It is well known that many of the common disorders that affect humans have a genetic component. The mapping of diseases having a Mendelian genetic transmission mechanism has led to major breakthroughs in our understanding of some of these diseases. In some animal species, one or several genes have been implicated in determining a shorter or longer life (Chapters 4 and 5). With respect to aging, some of the breakthroughs to come from recent human gene mapping

*I have led to a better insight into the role of genes as well as into the role of environmental factors on growth, development, and aging,
*I have served as a comprehensive guide to a large number of common human disorders,
*I may, by controlling for genetic susceptibility, improve our ability to identify and characterize additional genes, risk factors, and gene-to-gene as well as gene-to-environment interactions, and
*I may generate successful therapies identifying interventions that can improve the genotype of the susceptible individual.

The environment supplies the external and internal factors that make growth, development, and aging possible and allow inherited potentials to find expression. External factors, such as temperature, humidity, atmospheric gases, drugs, infections, and radiation

*I may condition the appearance of and modify the type of genetic expression and alter genetic composition to make possible the creation of new inheritable characters (mutations),
*I operate throughout the life span, and
*I may generate successful therapies by modifying physical, social, and economic conditions (e.g., better lifestyle, hygienic habits, education, more efficient adaptability).

Internal factors, such as hormones, nutrition, immune reactions, and nervous system signals may modify metabolic and homeostatic conditions leading to better adaptation to stress, for example (Chapter 9).

What are the respective influences of genetic and environmental factors in determining the phenotype? In humans, the best currently available method for estimating the involvement of genetic and environmental factors in determining or influencing the life span is through studies of twins and adopted children. For example, in a study of a large group of identical or fraternal twins, reared together or separately, heritability was calculated by intrapair differences or similarities in the mortality rates in terms of age at death. From the data reported, genetic factors accounted for one-third of the variance in longevity, and environmental factors for the remaining two-thirds (35). The evidence that genetic factors played, a relatively minor role, especially in twins who died at a young age, merits further examination (36).

One of the main characteristics of animals is their capacity to adapt to an ever-changing environment. Adaptation is attained through a series of physiologic adjustments (regulated by neuroendocrine signals) that serve to restore the normal state after it has been disrupted by altered external conditions that generate “stress” (Chapter 9). Adjustments to stress are grouped under the terms homeostasis, allostatics, and hormesis, and a large part of physiology is concerned with neurologic, endocrine, and immune regulatory mechanisms (e.g., negative and positive feedbacks) that coordinate the responses to stress and, ultimately, are responsible for survival. By the mature stage, many such adjustments are completed in humans. Stress throughout life plays a dual role: it may improve overall functional competence by stimulating and coordinating the various functions of the body to better adapt—a stimulation called hormesis (Chapter 9); or, in cases of repeated and severe stress, homeostasis may fail to occur or may be disrupted. In such cases, the terms “allostasis” and “allostatic load” refer to the sum of all untoward consequences of stress that may contribute to disease and, ultimately, death (Chapter 9).

Largely due to progress in physiotechnology (3), fantastic possibilities are now open of pursuing many avenues of research in humans, ranging from new reproductive technologies to cloning to genetic therapies and to a fuller understanding of the aging process. According to functional genomics (37–39), the early image we held of a stable gene is being replaced by one that is dependent on developmental interactions and environmental influences (40,41). In addition, “chance variation,” that is, variation due to neither genome nor environment, may play a significant role in development and aging. Many types of wild or inbred laboratory animals, for example, have almost identical genes and environments, and yet they exhibit a wide range of life spans (Chapters 3 and 4). Likewise, human identical twins are not truly identical. The early image we held of a stable gene is being replaced by one that is dependent on developmental interactions and environmental influences (40,41). In addition, “chance variation,” that is, variation due to neither genome nor environment, may play a significant role in development and aging. Many types of wild or inbred laboratory animals, for example, have almost identical genes and environments, and yet they exhibit a wide range of life spans (Chapters 3 and 4). Likewise, human identical twins are not truly identical. The effects of environmental factors are expressed in the heterogeneity of aging processes and may find their origin during development. The remarkable heterogeneity of the elderly population may result from the variability of genetic systems, the exposure to specific environmental conditions, and random variations (42,43). Each should be an object of future studies as, together, they may determine, influence, predispose, and increase susceptibility to aging and disease (Chapter 3).

REFERENCES


