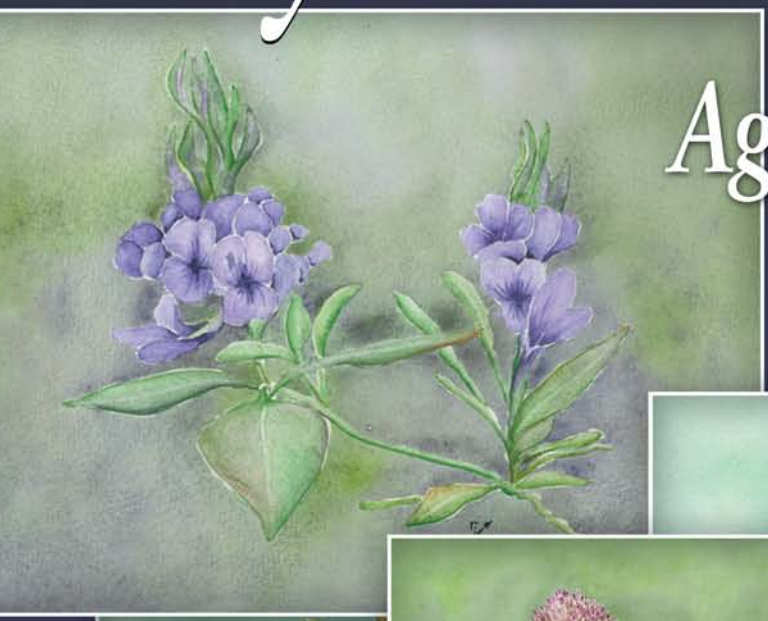
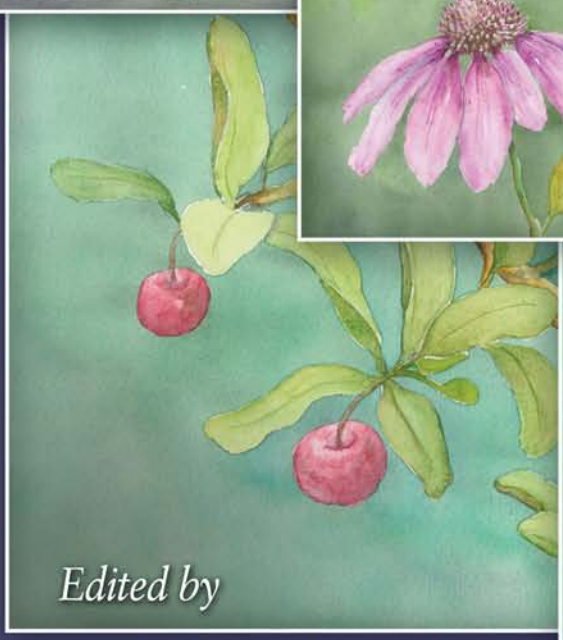
Phytochemicals

Aging and Health





Edited by

Mark S. Meskin
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Preface

Living healthier, longer lives is an almost universal value shared by most of the world's peoples. Both developed and developing societies around the globe are experiencing ever expanding populations of elderly and accumulating all the health-care burdens associated with aging populations. Interventions to help individuals remain healthy and active as they age are at the top of health providers' lists of priorities. Underpinning these public health and consumer interests is a large and growing body of research directed toward the science of healthy aging. A key component of this field of investigation is focused on elucidating the role of nutrition, plant-based diets, and phytochemicals in the aging process. This research has grown out of a substantial body of observational data pointing to lower risk of multiple chronic degenerative age-related diseases that are associated with the consumption of diets abundant in fruits, vegetables, and whole grains. Current research increasingly employs prospective and controlled clinical intervention studies to further elucidate the association between a plant-rich diet and a decreased risk of age-related degenerative conditions.

The 6th International Phytochemical Conference, "Phytochemicals: Aging and Health," was held in Buena Park, California on October 16 and 17, 2006. The conference was a joint effort of California State Polytechnic University (Cal Poly Pomona) and The Nutrilite Health Institute. This conference was the sixth collaboration between the two institutions, which have sponsored biennial international phytochemical conferences since 1996. Updated and expanded proceedings from the five previous international phytochemical conferences have been published: *Phytochemicals: A New Paradigm* (1998), *Phytochemicals as Bioactive Agents* (2000), *Phytochemicals in Nutrition and Health* (2002), *Phytochemicals: Mechanisms of Action* (2004), and *Phytochemicals: Nutrient–Gene Interactions* (2006). The organizers of the international phytochemical conference series invite well-known and respected researchers to discuss a chosen theme; "aging and health" was the theme of the 2006 conference. In each of the conferences, at least half of the presentations addressed the chosen theme. The remainder of the invited presentations covered new aspects of research methodology, real-world applications, and updates or expansions of previously introduced topics.

Presentations at the 6th International Phytochemical Conference began with a keynote address on prevailing theories of aging (Chapter 1), followed by discussions of state-of-the-art methodology with respect to polyphenolic analysis, bioavailability, and metabolism (Chapters 2 and 3). They continued with research presentations on botanicals and inflammation (Chapter 4), phytochemicals and vision (Chapter 5), phytochemicals and brain function (Chapter 6), green tea formulations and skin health (Chapter 7), and phytochemicals and cardiovascular disease (Chapter 8). The interest generated by the 5th International Phytochemical Conference, "Phytochemicals: Nutrient–Gene Interactions," led to a follow-up discussion on the potential for applying nutrient–gene interaction research findings to individual dietary recommendations (Chapter 9). The final two conference presentations provided discussions

of commercialization of botanical products from concept through development and testing in the areas of allergy relief (Chapter 10) and inflammation (Chapter 11). The research presentations delivered at the 6th International Phytochemical Conference have been revised, updated, and, in some cases, expanded for this volume.

In Chapter 1, Timiras, author of the widely respected and extensively utilized *Physiological Basis of Aging and Geriatrics* (4th edition, 2007), gives her assessment of how we have achieved the recent significant gains in both longevity and quality of life as well as the problems associated with a rapidly expanding elderly population. In this chapter, Timiras challenges us to rethink our basic concepts of aging: "The now increasing evidence of the ability of older individuals to muster compensatory and even regenerative responses to aging-related changes well justifies a renewed theoretical and practical interest in the study of physiology of aging at the basic and applied levels." Timiras outlines six areas of research in the area of "life extension sciences" that have the potential to extend as well as to improve life in old age. One of the six areas is dietary manipulation, including a role for phytochemical medicinals or supplements.

Chen and Blumberg pose the following question in Chapter 2: "Are there age-related changes in flavonoid bioavailability?" These authors point out that a growing number of research studies have suggested that flavonoids may be linked to lower incidence of cardiovascular disease and some forms of cancer. They also make the important observation that "putative health benefits of flavonoids are critically dependent on their bioavailability, metabolism, distribution, disposition, and excretion—parameters that are now beginning to be fully characterized." While a great deal of discussion has taken place regarding the potential role of phytochemicals in disease prevention and health promotion, far too little discussion and research have addressed the pharmacokinetics of candidate phytochemicals. This failure to fully address pharmacokinetic issues has been a recurring theme in previous international phytochemical conferences and was addressed in several chapters in *Phytochemicals: Mechanisms of Action* (2004). Chen and Blumberg point out that "while the requirements for many nutrients change across the life cycle, data on the influence of age on the pharmacokinetics of flavonoids are sparse," such information is needed to understand the role of flavonoids in health and disease. These authors discuss what is known and unknown about flavonoid bioavailability and aging and suggest directions for future research.

As previously noted, epidemiological observations and *in vitro* studies suggest that not only polyphenols but also carotenoids may have health-promoting properties that might reduce risk of cardiovascular disease and certain cancers. However, as Koh and Mitchell point out in Chapter 3, "It is important to note that although flavonoids and carotenoids are implicated in the prevention of chronic disease, almost all attempts to assign health-promoting activity to the *in vitro* antioxidant action of any one specific compound of these phytochemicals have been unsuccessful." They also note that difficulties in interpreting intervention study data stem from such problems as "incomplete characterization of the test material, unvalidated biomarkers, and the lack of understanding of polyphenol bioavailability and metabolism." In order to move the science forward in this area, it is vital to understand and improve

the analytical methodology for characterization and quantification of polyphenols and carotenoids. Koh and Mitchell discuss trends in the analysis of these phytochemicals and identify areas for improvements in this chapter.

The elderly segment of the population consumes the largest variety and the highest quantity of therapeutic agents. Dey and colleagues observe that "in the areas of cancer, infectious, and inflammatory diseases that are mechanistically linked, about 60–75% of the new drugs developed during 1983–1994 were based on naturally occurring compounds. This is in spite of the fact that a majority of the phytochemicals produced by the 250,000 plant species of the world still remains unexplored." These authors also note the disappointing track record of synthetic drug development over the same period of time. One explanation for the lack of phytochemical exploration has been the inability to apply high-throughput screening (HTS) techniques to multicomponent botanicals. The HTS methods have primarily been utilized to test single active ingredients. However, in a postgenomic era with so many potential targets and so much information available, these authors believe it is time to revisit screening and developmental approaches for botanicals. Chapter 4 provides "a case study for screening anti-inflammatory botanicals and strategies to further develop the identified hits into advanced therapeutic leads."

Chapters 5 through 8 discuss the roles of various phytochemicals in both healthy aging and chronic disease. Hammond and Renzi discuss the characteristics and function of lutein and zeazanthin within the human retina in Chapter 5. Age-related cataract (ARC) and age-related macular degeneration (AMD) are significant problems for the elderly. It is important to try to understand the role of macular pigment in the retina and its role in protecting the eye from diseases such as ARC and AMD. The ability of lutein and zeazanthin supplementation to increase macular pigment could impact retinal health. Hammond and Renzi provide a thorough overview of the current research and discuss the current hypotheses regarding protection from and prevention of disease in the eye.

One of the most common forms of dementia that affects the elderly population is Alzheimer's disease. In Chapter 6, Bastianetto and Quirion consider the possible neuroprotective effects of polyphenolic compounds. "Epidemiological studies have shown that consumption of fruits, vegetables, green tea, and red wine (in moderation) reduces the incidence of developing neurodegenerative diseases, including Alzheimer's disease. Polyphenols that are abundant in these foods and beverages likely contribute to their beneficial effects." These authors discuss hypothesized mechanisms for Alzheimer's disease and report on the results of experimental neuroprotective treatments utilizing polyphenols (particularly tea catechins and gallate esters).

In Chapter 7, Hsu discusses the possible preventative and therapeutic value of green tea in skin care and skin diseases. The author provides a brief history of green tea, identifies the key green tea polyphenols, reviews the hypothesized anticancer properties of green tea, and examines the prodifferentiation and anti-inflammatory properties of green tea polyphenols in skin cells. Hsu concludes that the experimental data "suggest that green tea polyphenols activate specific signal transduction pathways to regulate gene expression to accelerate terminal differentiation in the epidermis, in addition to their anticancer, antioxidant, and anti-inflammatory effects.

These effects not only are beneficial to many skin disorders, but also may provide anti-aging results."

Chapter 8 introduces a phytochemical source that had not been discussed at any of the five previous international phytochemical conferences. Pomegranate juice is a major source of polyphenolics and certain bioactive compounds in the juice have been shown to be bioavailable. Aviram and his colleagues provide a detailed discussion of the antioxidant activity of pomegranate juice polyphenols and review the results of studies of these polyphenols on the development of atherosclerotic lesions in both mice and humans. "All these antioxidative and anti-atherogenic effects of pomegranate polyphenols were clearly demonstrated *in vitro*, as well as *in vivo* in humans, and in the atherosclerotic apolipoprotein E-deficient mice. Dietary supplementation of pomegranate juice rich in polyphenols to patients with severe carotid artery stenosis or to atherosclerotic mice resulted in a significant inhibition in the development of the atherosclerotic lesions." Aviram and colleagues believe that their results suggest that combinations of antioxidants such as those found in pomegranate juice might be a better model for treatment than single antioxidants would be.

The 5th International Phytochemical Conference and the subsequent book, *Phytochemicals: Nutrient–Gene Interactions* (2006), generated a great deal of interest in nutrigenomics (the effects of bioactive dietary compounds on the expression of genes, proteins, and metabolites) and nutrigenetics (the effects of genetic variations on nutrient influences on health and disease of an individual). The field of nutrition science has always held out the hope of individualized dietary advice. However, for most of the history of nutrition science, dietary advice has been anything but "individualized." With the completion of the Human Genome Project and numerous research reports of nutrient–gene interactions, it may actually be possible to begin providing truly individualized nutrition advice. Chapter 9 explores this possibility; its objective is "to examine the feasibility, within the context of our current state of inquiry into nutrient–gene interactions, of using genetic information as cues upon which to base specific nutritional recommendations." The conclusions drawn by Vakili and colleagues are very interesting.

The final two chapters are an important part of the vision of the organizers of the international phytochemical conference series. The organizers hope to stimulate thoughtful and sound scientific research on the role of phytochemicals in disease prevention and health promotion. In addition, the organizers also want to encourage the development of commercial products based on solid research hypotheses and appropriate testing protocols. We would like to play a role in exposing industry to high-quality models of how to develop and test potentially valuable phytochemical products. Chapters 10 and 11 give two such examples.

In Chapter 10, Lemay and colleagues describe the development of a botanical combination product for allergy symptoms. First the authors describe a screening process to identify promising individual and combination botanicals with anti-allergic action. A selection of candidate compounds was then further screened utilizing skin-patch testing with human volunteers. The results of the second round of screening were used to formulate a potentially effective botanical combination formula. The finalized formulation was then tested in a double-blind, placebo-controlled clinical

trial. Lemay and colleagues report on the outcome of this developmental process and suggest that it is "a model for achieving market entry and general market competitiveness of innovative technologies and products in the dietary supplement field."

Chapter 11 presents a different type of model for the development of an innovative therapeutic product. Randolph discusses the application of nutrigenetic principles (see discussion of these principles in Chapter 9) to the creation of a product that can modulate or positively alter certain physiological parameters in a person due to the existence of specific polymorphisms in that individual. One option (as discussed in Chapter 9) might be to make dietary changes, while another would be to develop a botanical therapeutic agent. In this chapter, Randolph discusses the development program strategy and the data from a pilot clinical trial.

We believe the research presented in this book should be of interest to a broad audience of food scientists and food technologists, researchers interested in phytochemicals, food industry innovators, nutrition scientists and nutritionists, and other allied health professionals. Phytochemical research is still in its infancy and it is the goal of these chapters to promote high-quality science and stimulate creative thought.

Mark S. Meskin

Acknowledgments

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The editors would like to thank Randy Brehm for all her support and constant encouragement of this project. We would also like to thank Judith Simon and the editorial staff at Taylor & Francis Group for their patience and excellent work.

The Editors

Mark S. Meskin, Ph.D., R.D., is professor and director of the Didactic Program in Dietetics in the Department of Human Nutrition and Food Science, College of Agriculture, at California State Polytechnic University, Pomona. Dr. Meskin has been at Cal Poly Pomona since 1996.

Dr. Meskin received his bachelor of arts degree in psychology from the University of California, Los Angeles (1976), his master of science degree in food and nutritional sciences from California State University, Northridge (1983), and his Ph.D. degree in pharmacology and nutrition from the University of Southern California School of Medicine (1990). In addition, he was a postdoctoral fellow in cancer research at the Kenneth Norris, Jr., Cancer Hospital and Research Institute, Los Angeles (1990–1992). He received his academic appointment at the University of Southern California School of Medicine (1992) and served as assistant professor of cell and neurobiology and director of the nutrition education programs (1992–1996). While at the University of Southern California School of Medicine, he created, developed, directed, and taught in the master's degree program in nutrition science. Dr. Meskin has also served as a faculty member of the Department of Family Environmental Sciences at California State University, Northridge, and the Human Nutrition Program at the University of New Haven, Connecticut. He has been a registered dietitian since 1984 and is also a certified nutrition specialist (1995).

Dr. Meskin has been involved with both the local and national Institutes of Food Technologists (IFT) for more than 25 years. He is a past chair of the Southern California IFT and remains involved in the group. Dr. Meskin has been an active food science communicator for the national IFT, was a member of the IFT/National Academy of Sciences Liaison Committee, and has served as a member of the IFT Expert Panel on Food Safety and Nutrition. He is also involved in several IFT divisions, including the Nutrition, Toxicology & Safety Evaluation; Biotechnology; Nutraceutical and Functional Foods; and Religious & Ethnic Foods divisions.

Dr. Meskin served as a science advisor to the Food, Nutrition and Safety Committee of the North American branch of the International Life Sciences Institute for a 3-year term (2000–2002). He has been a long-time member of the advisory board of the Marilyn Magaram Center for Food Science, Nutrition and Dietetics at California State University, Northridge. Dr. Meskin was involved with the Southern California Food Industry Conference for many years as an organizer, chair, moderator, and speaker. He has also served as a member of the medical advisory board of the Celiac Disease Foundation.

Dr. Meskin is regularly invited to speak to a wide variety of groups and has written for several newsletters. He has been a consultant for food companies, pharmaceutical companies, HMOs, and legal firms. He is a member of many professional and scientific societies, including the American Dietetic Association (dietetic educators of practitioners; sports, cardiovascular, and wellness; women's health and reproductive nutrition; and vegetarian nutrition practice groups), the American Society for Nutrition, the American College of Nutrition, the American Council on Science and

Health, the Institute of Food Technologists, and the National Council for Reliable Health Information.

Dr. Meskin's major areas of research interest include: (1) hepatic drug metabolism and the effects of nutritional factors on drug metabolism and clearance; (2) nutrient–drug interactions; (3) the role of bioactive non-nutrients (phytochemicals, herbs, botanicals, and nutritional supplements) in disease prevention and health promotion; (4) fetal pharmacology and fetal, maternal, and pediatric nutrition; (5) nutrition education; and (6) the development of educational programs for improving science literacy and combating health fraud.

Dr. Meskin has coedited five books on phytochemical research, including *Phytochemicals: A New Paradigm* (1998), *Phytochemicals as Bioactive Agents* (2000), *Phytochemicals in Nutrition and Health* (2002), *Phytochemicals: Mechanisms of Action* (2004), and *Phytochemicals: Nutrient–Gene Interactions* (2006). He is a member of numerous honor societies, including Phi Beta Kappa, Pi Gamma Mu, Phi Kappa Phi, Omicron Nu, Omicron Delta Kappa, Phi Upsilon Omicron, Gamma Sigma Delta, and Sigma Xi. He was elected a fellow of the American College of Nutrition in 1993 and was certified as a charter fellow of the American Dietetic Association in 1995. He received the Teacher of the Year award in the College of Agriculture in 1999 from Cal Poly Pomona, the Advisor of the Year award in the College of Agriculture in 2002, and the advisor of the year award from Gamma Sigma Delta (national agriculture honor society) in 2004.

Wayne R. Bidlack, Ph.D., is a professor in the Department of Human Nutrition and Food Science and has return rights to the Department of Animal and Veterinary Sciences, California State Polytechnic University, Pomona.

Dr. Bidlack received his bachelor of science degree in dairy science and technology from the Pennsylvania State University (1966), his master of science degree in food science from Iowa State University (1968), and his Ph.D. degree in biochemistry from the University of California, Davis (1972). In addition, he was a postdoctoral fellow in pharmacology at the University of Southern California School of Medicine (1972–1974). He received his academic appointment at the University of Southern California (1974), serving as assistant dean of medical student affairs (1988–1991) and as professor and interim chair of pharmacology and nutrition (1991–1992). Dr. Bidlack has also served as chairman and professor of food science and human nutrition and as director of the Center for Designing Foods to Improve Nutrition at Iowa State University, Ames, from 1992 to 1995. He was appointed dean of the College of Agriculture at California State Polytechnic University, Pomona, serving from 1992–2007.

Dr. Bidlack has been a professional member of the Institute of Food Technologists for more than 30 years. He has served as a member of the annual program committee, as a member of both the Expert Panel on Nutrition and Food Safety and the Scientific Lectureship Committee, and as a scientific lecturer. He was program chairman and chairman of the IFT Toxicology and Safety Evaluation Division (1989–1990) and has served as a member of the Executive Committee for both the TaSE Division and the Nutrition Division. He has served as editor of the TaSE newsletter. For the Southern

California section of IFT, Dr. Bidlack has served as councilor, chairman of the scholarship committee, program chairman, and chairman of the section (1988–1989). He has also served as regional communicator for IFT in Southern California. Dr. Bidlack was elected a fellow of IFT in June 1998 and elected as counselor representative to the Executive Committee (2000–2003). He served on the finance committee (2003–2006) and as the chairman of the Strategic Planning Committee (2004–2007). Currently, he chairs the Audit Committee (2006–2009) and is chair of the committee on "making food safety decisions when the science is incomplete."

Dr. Bidlack is past president of the Food Safety Specialty Section of the Society of Toxicology, served on the International Life Sciences Institute Committee on Nutrition and Food Safety, and held the position of scientific advisor for the subcommittee on iron and health and the subcommittee on apoptosis related to fumonisin toxicity. He has also served as a member of the board for the Certification Board for Nutrition Specialists and actively contributed to the creation of the national certification exam. In addition, he is serving on the editorial board and as book editor for the *Journal of the American College of Nutrition*. He served as an editor of two books on phytochemicals published by Technomics and four others published by CRC Press; the seventh in the series is in press. He continues to review grants for several agencies and universities. Currently, Dr. Bidlack is serving as a member of the board of the California Department of Food and Agriculture.

In 1990, Dr. Bidlack received the meritorious service award from the California Dietetic Association and the distinguished achievement award from the Southern California Institute of Food Technologists. He was awarded honorary membership in the Golden Key, a national honor society, in 1995 and in Gamma Sigma Delta in 1998. He also received the Bautzer Faculty University Advancement Award for Cal Poly Pomona in 1998. In 2002, Dr. Bidlack was awarded the CSU WANG Family Excellence Award for Administrators. The Cal Poly Pomona chapter of Gamma Sigma Delta awarded Dr. Bidlack the outstanding faculty–administration award for 2003.

Dr. Bidlack's research interests are varied and integrate the general areas of nutrition, biochemistry, pharmacology, and toxicology. He maintains interest in the development of value-added food products, evaluation of biologically active food components (both plant and animal), and use of commodities for nonfood industrial uses. From these efforts, Dr. Bidlack has published more than 55 publications and 12 book chapters; he has edited seven books. He has been elected to several national scientific societies, including the American Institute of Nutrition (American Society of Nutritional Science), the American College of Nutrition (certified nutrition specialist), the Institute of Food Technologists, the American Society of Pharmacology and Experimental Therapeutics, and others.

Finally, Dr. Bidlack has served the food industry as a consultant in a number of areas, including as an advisor to the California Avocado Commission (serving on the Nutrition Committee) and the California Egg Commission on food safety issues.

R. Keith Randolph is the manager of the Analytical Services Department at Access Business Group in Ada, Michigan. He has oversight of a team of 44 chemists,

engineers, and biologists who provide technical support for discovery, quality assurance, development, and manufacturing of consumer products distributed and sold through the Amway business worldwide. He has guided the planning and implementation of Nutrilite Health Institute's international phytochemical conference for the past 6 years.

Dr. Randolph came to Access Business Group in 2000 with 17 years of combined experience in teaching and basic research at the State College of New York, Stony Brook; the Medical College of Pennsylvania in Philadelphia; and the Cleveland Clinic Research Foundation in Cleveland, Ohio. He is first author on 18 original research publications in the areas of lipid biochemistry, metabolism, nutrient–gene interactions, cardiovascular disease, and skin physiology. He has served as editor for three books. He is a fellow of the American College of Nutrition. He also holds memberships in the American Society for Nutritional Sciences, American Chemical Society, American Society for Molecular Biology and Biochemistry, and the Association of Analytical Communities.

Dr. Randolph earned a bachelor of science degree in chemistry and biology from Wayland College in Texas. He also holds a Ph.D. in experimental pathology from the Bowman Gray School of Medicine at Wake Forest University in Winston-Salem, North Carolina. He was introduced to his scientific career in clinical laboratory science at the Armed Forces Academy of Health Sciences, San Antonio, Texas during a 4-year tour of duty in the U.S. Army between 1972 and 1976.

Dr. Randolph is the father of three sons, Matt, Parker, and Taylor, all of whom are in college in Texas. He is married to Susan Randolph, who, as a registered dietitian, shares his passion for nutrition and health. In his spare time, Dr. Randolph seriously pursues watercolor art. He extracts pigments for his art from plant materials, most notably flower blossoms. His art has been exhibited in New York and California.

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CHAPTER 1

Technophysiology, Evolution, and Aging
Toward a New Image of Aging

Paola S. Timiras

CONTENTS

TECHNOPHYSIOLOGY, EVOLUTION, AND AGING

The increase of human population and the extension of human longevity, both worldwide, represent perhaps the two greatest human achievements that have occurred from prehistoric to current times. In this introductory chapter, the biological consequences of this historical extension in human longevity are considered within the context of those factors and conditions that may contribute to promote longevity and quality of life in old age. Thanks to improving life conditions stemming from advances in agricultural practices, followed by progress in industry and technology, the life span has lengthened from 20–35 years in early history to 45–50 years in 1900 and to 80 years and longer at the beginning this twenty-first century.[1–3]

Thus, in the world's healthiest countries, approximately one-half of the increase in average life span has occurred during the twentieth century and persists in the twenty-first.[4] Continuing progress in longevity may be attributed to (1) public health reforms and improved hygiene, (2) advances in medical knowledge and practices,

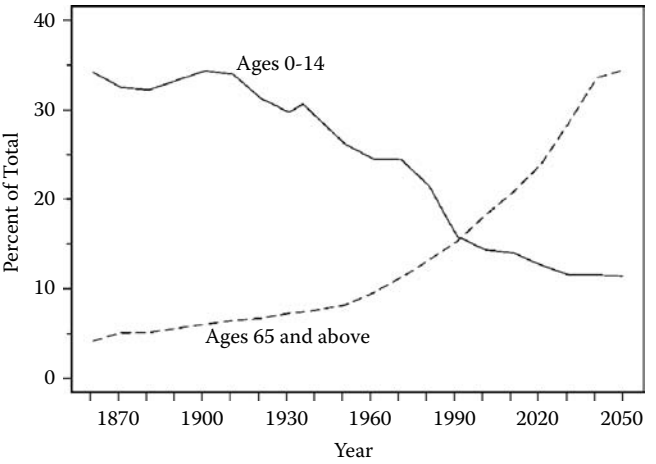

Figure 1.1 Proportion of the population aged 0–14 versus 65+ years of age, in Italy, 1861–2050. Note: The increase in the proportion of the old population has crossed over the decline in the proportion of the younger population in the early twenty-first century. Figures for 2001–2050 are projections. (From Timiras, P.S., *Physiological Basis of Aging and Geriatrics*, 4th ed., Informa Healthcare, New York, 2007. With permission.)

(3) better control of the environment, and (4) rising income and standards of living. Much of the increase in average life span has been ascribed not only to extended longevity, but also, in the most developed countries, to the near elimination of infant mortality (Figure 1.1).[5–7] Notwithstanding the improvement of survival at birth, the proportion of young people in the total population has decreased and continues to decline in most developed countries; this decline is primarily attributable to reduced fertility due to various socioeconomic and lifestyle factors. This is illustrated in the case of Italy, where the average family had five or six children in 1900, compared to one child currently (Figure 1.1). The challenge of a larger proportion of older than of younger people in the population demands "that societies reorient themselves toward the care of a large, dependent population at the end of life rather than at the beginning. Such adjustments are not without costs as the needs of children and of the elderly are quite different."[4] Therefore, careful social and biomedical adjustments and planning are required to provide for this significant shift in population distribution from younger to older ages.

In the United States, more people now live a longer average life span, and it has been forecast that this trend may continue.[5–7] For example, it has been predicted that by the year 2030 about one-fifth (18%) of the population will live to be 65 years or older (Figures 1.2 and 1.3). The increase—from 2.7% men and 3.8% women in 1900 to 15.2% men and 26.6% women in 2002—in probability that 50-year-old men and women may live to 90 years of age further illustrates the plausibility of this trend (Figure 1.4).