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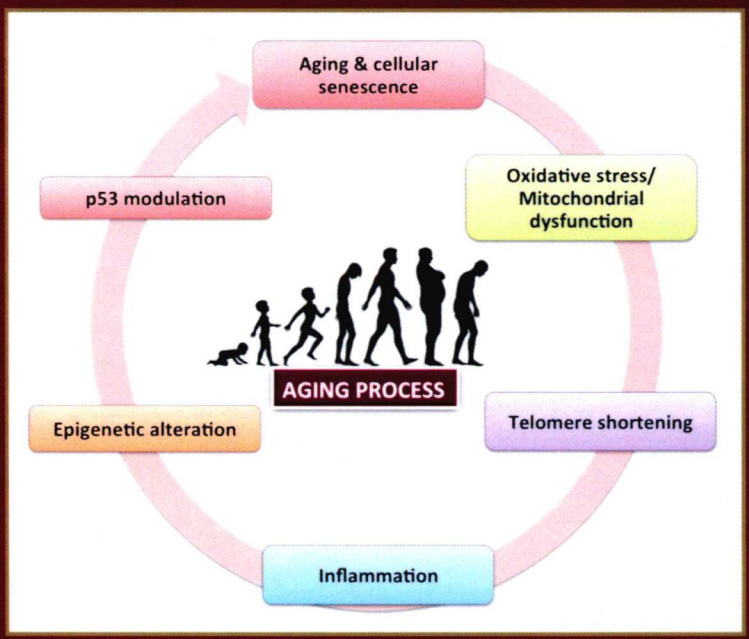
EDITED BY

P. HEMACHANDRA REDDY



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Molecular Biology of Aging

Edited by

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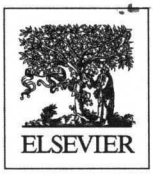

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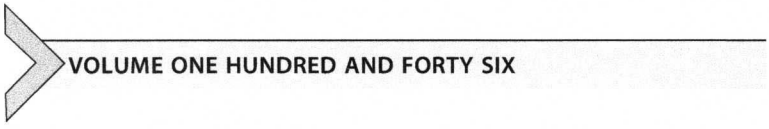
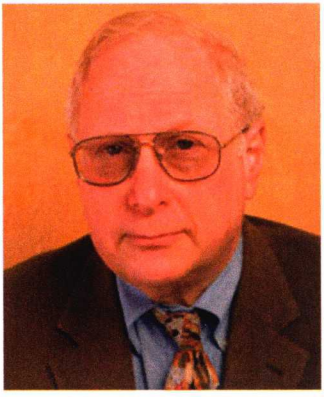


PROGRESS IN MOLECULAR BIOLOGY AND TRANSLATIONAL SCIENCE

Molecular Biology of Aging

IN MEMORIAM
P. Michael Conn, PhD



P. Michael Conn unexpectedly passed away on Saturday, November 26, 2016 in Lubbock, TX, United States. Dr. Conn was a pioneer in the field and a role model with great dedication to scientific discovery. At Texas Tech University Health Sciences Center (TTUHSC), Dr. Conn was an outstanding and highly respected researcher, educator, leader, director, consultant, and manager of university programs. He elevated the TTUHSC research mission by supporting its scientists across disciplines, departments, and schools.

He received his Bachelor of Science and a teaching certificate from the University of Michigan (1971), a Master of Science from North Carolina State University (1973), and a doctorate from Baylor College of Medicine (1976). Dr. Conn received a postdoctoral fellowship to study the endocrine research methods at the National Institutes of Health in Bethesda, MD (1976–78). He then joined the faculty of the Department of Pharmacology at Duke University Medical Center (1978) as an assistant professor and was promoted to associate professor in 1982. In 1984, Dr. Conn went to the University of Iowa College of Medicine, where he accepted a position as professor and head of the Department of Pharmacology, a position he held for 11 years.

Dr. Conn joined TTUHSC in December 2013 as the Senior Vice President for Research. He was also Associate Provost and the Robert C. Kimbrough Professor of Internal Medicine at TTUHSC, with joint appointment in the Department of Cell Biology and Biochemistry. He was previously the Director of Research Advocacy at TTUHSC. Before coming to TTUHSC, Dr. Conn was a professor in the Departments of Physiology and Pharmacology, Cell Biology and Development, and Obstetrics and Gynecology at the Oregon Health and Science University, and a senior scientist at the Oregon National Primate Research Center. Dr. Conn served for 12 years as a special assistant to the primate center director before becoming Associate Director.

For nearly 40 years, he was a leading scientist in elucidating the function of the G protein-coupled receptor in the gonadotropin-releasing hormone receptor system. Dr. Conn's research led to a better understanding of therapeutic targets to help patients with endocrine disease.

Dr. Conn was the first to report that membrane receptors, when they bound to agonists, but not to antagonists. Dr. Conn's research into membrane receptors changed the way these proteins were viewed by the scientific community.

Another line of research that Dr. Conn pursued was receptor–receptor interactions. This research contributed to our understanding of the function of membrane receptors, and it led to what was then called microaggregation—the massing of receptor dimers, which Dr. Conn distinguished from macroaggregation. Dr. Conn's research into membrane receptors and their interactions led to the development of oligomerization, a chemical process that converts molecular aggregates into molecular complexes. This process is important for our present understanding of how receptors regulate and communicate information to other receptors. Dr. Conn also contributed significantly to the scientific community's understanding of the use of diacylglycerols, which are lipids. Working with Jim Neidel, Dr. Conn revealed how these lipids are involved in hormonal action.

Dr. Conn demonstrated that many receptor mutations result in the misrouting of molecules. With this information, Dr. Conn developed a treatment strategy that restores mutant receptors to function. This strategy appears useful in restoring a range of mutant receptors to normal function, including receptors in cystic fibrosis, nephrogenic diabetes insipidus, hypercholesterolemia, retinitis pigmentosa, and a range of digestive diseases. Dr. Conn also created high-throughput screening, a drug-discovery process widely used in the pharmaceutical industry, to automatically assay the biochemical activity of drug-like compounds, from which chemical libraries are formed. Dr. Conn's research into high-throughput screenings has resulted in the appreciation of pharmacoperone drugs as a new class of drugs to treat abnormal receptors.

Dr. Conn authored or coauthored over 350 publications in receptor research, and he wrote or was the editor of over 200 books, including text books on neuroscience, molecular biology, and endocrinology. Dr. Conn served as the editor of many professional journals and book series, including *Endocrinology*, *Journal of Clinical Endocrinology and Metabolism*, *Endocrine*, *Methods*, *Progress in Molecular Biology and Translational Science*, and

Contemporary Endocrinology. Dr. Conn was also a member of numerous study sections, and advisory committees and groups: 1986–87, *Biochemical Endocrinology*; 1991–95, *Pharmacological Sciences*; 1985–89, American Society for Cell Biology, Council Member; 1992–97, The Endocrine Society, Council Member; 1996, The Endocrine Society, President; 1997–2000, The Hormone Foundation Board of Directors; 1998–2000, National Diabetes Education Program Steering Committee; 1995–2002, Pituitary Tumor Network Association Scientific Advisory Committee; and 2000–02, FASEB Board of Directors.

Dr. Conn served on the National Board of Medical Examiners, including 2 years as the Chair of its Reproduction and Endocrinology Committee, and he was on the Board of Scientific Councilors for the Intramural Program in NICHD at the National Institutes of Health. Dr. Conn was a member of Council for the American Society for Cell Biology and the Endocrine Society, and he was a former president of the Endocrine Society, during which time he founded the Hormone Foundation and worked with political leaders throughout the United States to heighten the public's awareness of diabetes. Dr. Conn was an elected member of the Mexican Institute of Medicine and a fellow of the American Association for the Advancement of Science.

In recognition of Dr. Conn as an extraordinary scientist and educator, he received many awards and honors. Dr. Conn's students and fellows have gone on to become leaders in industry and academia. Dr. Conn was given a MERIT award from the National Institutes of Health; the J.J. Abel Award of the American Society for Pharmacology and Experimental Therapeutics; the Weitzman, Oppenheimer and Ingbar Awards of the Endocrine Society; the National Science Medal of Mexico (the Miguel Aleman Prize); and the Stevenson Award of Canada. He was also the recipient of the Medical Research Foundation Oregon Award for Discovery, the Media Award of the American College of Neuropsychopharmacology, and a distinguished alumnus of Baylor College of Medicine. Dr. Conn's honors included the Dean's Award from TTUHSC, bestowed upon him for outstanding work as a scientist.

P. Michael Conn was our friend, teacher, and mentor, and we will miss him dearly.

P. Hemachandra Reddy, PhD

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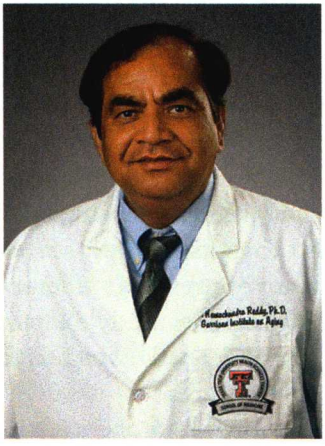
PREFACE



The biology of aging is a topic that has long interested me. When I was child, I witnessed my grandfather dying at the relatively young age of 55 years. And my father died at 61 years of age. These losses have led me to try to answer why some people die so early and others live so long, 90 years and beyond. What are factors that cause early death? Are they genetic or environmental, or both? Is lifestyle the main factor that may shorten a life span?

In this modern era, with medical and technological advancements and with increased social media about health care, I am appreciative that longevity is increasing, but not without costs. Dementia rates in persons older than 80 years are alarmingly increasing in many populations of the world. It is important to better understand the biology behind aging and the aging brain. And it is also important to identify biomarkers of aging in order to develop effective therapeutic strategies.

There has been much research on aging and age-related diseases, and important contributions to better understanding the molecular biology of aging. This area is too broad to cover fully in this book or in a few books. I have narrowed the scope of this book to four topics under the rubric of molecular biology of aging: (1) molecular, cellular, and physiological bases of metabolic syndromes, including diabetes, obesity, and Alzheimer's disease; (2) the role of mitochondria in aging and Alzheimer's disease; (3) the role of microRNAs in aging and age-related human neurological diseases; and (4) the aging kidney and its physiological and pathological implications for diabetes.

Chapters 1, 2, and 8 primarily cover basic biology, and cellular and therapeutic aspects of metabolic syndromes, including diabetes, obesity, and Alzheimer's disease. In the first chapter, John Culberson covers morbidity in chronic diseases, with a focus on the role of aging and age-related chronic diseases, such as sarcopenia. Sarcopenia is an age-related loss of skeletal muscle mass, which is accelerated by chronic inflammation. Sarcopenia results in

a cascade of cytokines, insulin resistance, hyperglycemia, and altered mitochondrial glucose signaling pathways. Dr. Culberson also covers neurogenesis and defective neuronal plasticity in the diabetic brain and advanced glycation end-products generated by chronic hyperglycemia identified in postmortem brains of persons with Alzheimer's disease.

In the second chapter, Jasvinder Singh Bhatti and colleagues discuss several features of metabolic disorders, particularly the involvement of mitochondrial dysfunction and oxidative damage in aging and age-related metabolic and neurodegenerative disorders. They focus on the structure, function, and physiology of mitochondria in such disorders as diabetes, obesity, cardiovascular diseases, and stroke. They also cover therapeutic strategies for mitochondrial dysfunction and oxidative stress in different age-related metabolic disorders, including such strategies as lifestyle intervention, and pharmacological and mitochondria-targeted therapeutic approaches.

Subbiah Pugazhenthi's chapter focuses on cellular changes in obesity, diabetes, hypertension, and cardiovascular disease. He describes risk factors for comorbidities, collectively referred to as the *metabolic syndrome*. This syndrome can play a critical role in driving neuroinflammation, an important factor of Alzheimer's disease pathogenesis. His research suggests a role for microglia, the resident immune cells of the brain, in Alzheimer's disease pathogenesis. Metabolic syndrome could reactivate microglia through the interface of blood–brain barrier. As Dr. Pugazhenthi notes, an age-dependent breakdown of the blood–brain barrier has been found in humans with neurological diseases, including those with Alzheimer's disease.

Chapters 6, 7, 9, and 11 focus on mitochondrial abnormalities and mitochondrial dysfunction, and protective effects of mitochondria-targeted antioxidants. In Chapter 6, Arubala P. Reddy and P. Hemachandra Reddy present a systematic review of mitochondria-targeted antioxidants and a summary of antioxidants that researchers have used in studying mouse models of Alzheimer's disease, elderly populations, and clinical trials involving patients with Alzheimer's disease. They also discuss recent progress in the development and testing of mitochondria-targeted molecules, using cell cultures and mouse models of Alzheimer's disease. They cover mitochondria-targeted molecules as potential therapeutic targets to delay or prevent the progression of Alzheimer's disease.

In Chapter 7, Peter Rabinovitch and colleagues discuss catalase mouse models that they have developed in order to understand the role of catalase in delaying aging. They describe three lines of mice—mice overexpressing

catalase targeted to mitochondria (mCAT), peroxisomes (pCAT), and the nucleus (nCAT) that they have developed to investigate the role of hydrogen peroxide in aging. They review features of all three mouse models, noting that the mCAT mice have the longest and healthiest life span. Dr. Rabinovitch's group extensively studied mCAT mice and reviewed well in their chapter.

In Chapter 9, Russell Swerdlow and colleagues describe mitochondrial and bioenergetic functional changes in aging and Alzheimer's disease. They link mitochondrial and bioenergetic impairments to the aging brain, and they discuss a new avenue that involves transferring mitochondria from patients with Alzheimer's disease to cell lines depleted of endogenous mitochondrial DNA, in order to develop cytoplasmic hybrid cell lines of mice that exhibit specific biochemical, molecular, and histologic features of Alzheimer's disease. They also discuss their proposed mitochondrial cascade hypothesis that places mitochondrial dysfunction at the apex of the pathology pyramid for Alzheimer's disease.

In Chapter 11, Shirley ShiDu Yan and colleagues provide a review of major recent findings on mitochondrial abnormalities and synaptic dysfunction relevant to aging, neurodegeneration, and cognitive decline in persons with Alzheimer's disease and diabetes. Dr. Yan argues that elucidation of the role of mitochondrial perturbation can inform the development of specific small molecules capable of targeting aberrant mitochondrial function as a therapeutic delivery system for combating aging-related dementia and neurodegenerative diseases.

Chapters 3–5 focus on the role of microRNAs in aging and age-related diseases. In Chapter 3, Murali Vijayan and colleagues focused on ischemic stroke in aging and Alzheimer's disease, explaining that stroke and vascular dementia increase with an increase in a number of modifiable factors. They suggest that most strokes can be prevented or controlled through pharmacological and surgical interventions, and lifestyle changes. They also identify cellular changes that are implicated in ischemic stroke, including inflammatory responses, microRNA alterations, and marked changes in brain proteins. They review the latest developments of research that identifies protein biomarkers in peripheral and central nervous system tissues from aged persons.

In Chapter 4, Subodh Kumar and colleagues review research on the biogenesis of microRNAs and the role of miRNAs, particularly circulatory mRNAs, in detecting aging and neurodegenerative diseases, particularly Alzheimer's, Parkinson's, and Huntington's diseases. They hypothesize that,

at a pathological level, changes in cellular homeostasis lead to the modulation of molecular function in cells, resulting in the deregulation of miRNA expression. They suggest that identification of these changes may open a new avenue for developing biomarkers capable of detecting aging and cellular senescence.

In Chapter 5, P. Hemachandra Reddy and colleagues discuss several aspects of aging, including oxidative damage, mitochondrial dysfunction, telomere shortening, and inflammation, all of which leads to cellular senescence. Reddy and colleagues hypothesize that cellular senescence may induce age-related human diseases, including Alzheimer's, Parkinson's, multiple sclerosis, amyotrophic lateral sclerosis, cardiovascular, cancer, and skin diseases. They also discuss microRNAs in aging persons and persons with Alzheimer's disease, as possible blood-based peripheral biomarkers of Alzheimer's disease.

In Chapter 10, Hezekiah Sobamowo and Sharma Prabhakar cover the physiology and pathology of the aging kidney, noting that aging is linked to a progressive decline in renal function along with concurrent morphological changes in kidney, ultimately leading to glomerulosclerosis. They also discuss cellular changes in the aging kidney.

I sincerely thank all the contributors for their outstanding chapters. I also thank Magesh Mahalingham, Helene Kabes, and Alex White at Elsevier, for their support and help in assembling this volume. I also recognize and thank P. Michael Conn, PhD, posthumously for introducing me to the first volume in the series *Molecular Biology of Aging in the Progress in Molecular Biology and Translational Science*.

P. Hemachandra Reddy, PhD

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