UNAGING

Aging is a subject of concern to everyone, but is widely misunderstood. If we view it as inevitable, we miss the fact that not everyone is able to grow to an old age. Realization of this reality helps us to understand that aging presents a wonderful opportunity – an opportunity to make choices about how we live which can enhance the aging process and offer a chance to live to our potential.

This book clearly presents the four reserve factors (cognitive, physical, psychological, and social) which impact our ability to have healthy responses to the stresses of aging. By giving the biological basis for the advice given, you will learn the steps to take in your activities, diet, and mental outlook to grasp the opportunity that aging offers. Everyone must know that what we do makes a difference.

Robert Friedland MD is a neurologist and the Rudd endowed professor of Neurology and Neurobiology at the University of Louisville School of Medicine in Kentucky. He previously worked at the University of California, Berkeley, the US National Institute on Aging, and Case Western Reserve University. Recently his research has uncovered a key role of intestinal bacteria in the initiation and progression of Alzheimer’s disease, Parkinson’s disease, and amyotrophic lateral sclerosis. His studies of humans and animals in the United States, Japan, the Middle East, and Kenya have helped to advance the concept that the risk of aging-related brain diseases can be lowered through our personal actions.
“Rooted on his vast clinical and research experience, Dr. Friedland takes us on an accessible scientific tour to demystify the inevitability of aging. Dementia, he highlights with a wealth of examples, is not preordained in anyone, even in individuals with high-risk genetic mutations or with brain amyloid plaques. Dr. Friedland reviews the evidence accumulated to make his case that specific changes in our own environment can shape how we age – or not.”

Alberto Espay, author of *Brain Fables: The Hidden History of Neurodegenerative Diseases and a Blueprint to Conquer Them*

“Dr. Friedland’s idea that aging is not inevitable is not fully recognized by the general public. However, recent advances in geriatrics show that his idea ‘aging is not inevitable’ is correct. This book is impressive because he teaches us the mechanisms of aging and how to enhance aging. It’s possible to change your life from this book. I hope you will know the truth and gain a wonderful tool against aging.”

Professor Toshiki Mizuno, Kyoto Prefectural University of Medicine

“In his book, *Unaging*, Dr. Friedland begins by setting the stage, describing the importance of physical, mental, psychological, and social health, and explaining that the goal is not normal aging, but exceptional aging. He then teaches you how to attack and subdue the harmful habits that accelerate aging by extrapolating the results of rigorous scientific studies. This book is a ‘must read’ for anyone who would like to use the latest scientific studies to help them live healthier lives as they age.”

Andrew E. Budson, author of *Seven Steps to Managing Your Memory: What’s Normal, What’s Not, and What to Do About It*

‘You have to grow old but you don’t have to age. This is the book that tells you how to do it’

Nori Graham, author of *A Pocket Guide to Understanding Alzheimer’s Disease and Other Dementias*

With clear language and an attention-grabbing narrative style, Dr. Friedland introduces and discusses many of the issues related to aging that represent the pillars of the science on the subject. From an original perspective, the book addresses the so-called reserve factors, neurological diseases, mental health, and most importantly, the actions we need to take to improve our chances of a healthy and satisfactory aging, where aging is seen as a blessing, not as a burden. The book closes with the chapter “The opportunity of aging” which, in my interpretation, summarizes the author’s overview.

Anyone interested in aging should read this text.

Dr. Carmen García Peña, *Instituto Nacional de Geriatría*
Unaging
The Four Factors that Impact How You Age

ROBERT P. FRIEDLAND
This publication is in copyright. Subject to statutory exception and to the provisions of relevant collective licensing agreements, no reproduction of any part may take place without the written permission of Cambridge University Press.

First published 2022

Printed in the United Kingdom by TJ Books Limited, Padstow Cornwall

A catalogue record for this publication is available from the British Library.

Library of Congress Cataloging-in-Publication Data
Names: Friedland, Robert P., author.
Title: Unaging : the four factors that impact how you age / Robert P Friedland.
Identifiers: LCCN 2021063076 (print) | LCCN 2021063077 (ebook) | ISBN 9781009087742 (paperback) | ISBN 9781009083645 (ebook)
Classification: LCC RA776.75 .F74 2022 (print) | LCC RA776.75 (ebook) | DDC 613.2–dc23/eng/20220211
LC record available at https://lccn.loc.gov/2021063076
LC ebook record available at https://lccn.loc.gov/2021063077

Cambridge University Press has no responsibility for the persistence or accuracy of URLs for external or third-party internet websites referred to in this publication and does not guarantee that any content on such websites is, or will remain, accurate or appropriate.

Every effort has been made in preparing this book to provide accurate and up-to-date information that is in accord with accepted standards and practice at the time of publication. Although case histories are drawn from actual cases, every effort has been made to disguise the identities of the individuals involved. Nevertheless, the authors, editors, and publishers can make no warranties that the information contained herein is totally free from error, not least because clinical standards are constantly changing through research and regulation. The authors, editors, and publishers therefore disclaim all liability for direct or consequential damages resulting from the use of material contained in this book. Readers are strongly advised to pay careful attention to information provided by the manufacturer of any drugs or equipment that they plan to use.
To my patients and their current and future families.
# CONTENTS

List of figures and tables .......................... page x
Preface ................................................ xi

**PART I  FOUNDATIONS: WHAT DO WE NEED TO KNOW ABOUT OPTIMAL AGING?** 1

1 AGING IS NOT INEVITABLE, IT IS AN OPPORTUNITY  3

2 THE THEORY OF THE MULTIPLE RESERVE FACTORS 25

3 THE BRAIN IS NOT AN ORGAN, IT IS THE MASTER  42

4 MEMORY AND COGNITION ........................ 60

5 THE NEURODEGENERATIVE DISEASES OF AGING  76

6 STROKE AND VASCULAR COGNITIVE IMPAIRMENT 107

7 OTHER DEMENTIAS ................................. 117

8 OUR MICROBIOTA AND HOW TO DO GENE THERAPY IN THE KITCHEN 126

9 THE HEALTH OF THE BODY AND THE PHYSICAL RESERVE FACTOR 148
<table>
<thead>
<tr>
<th>CONTENTS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>10  DEPRESSION, ANXIETY, AND WHAT GOOD IS FEELING BAD?</td>
<td>161</td>
</tr>
<tr>
<td>11  GENETICS AREN'T EVERYTHING</td>
<td>170</td>
</tr>
<tr>
<td><strong>PART II APPLICATIONS: WHAT CAN WE DO ABOUT THE OPPORTUNITY OF AGING?</strong></td>
<td>183</td>
</tr>
<tr>
<td>12  OVERVIEW</td>
<td>185</td>
</tr>
<tr>
<td>13  PHYSICAL ACTIVITY</td>
<td>192</td>
</tr>
<tr>
<td>14  WHOLE BODY HEALTH</td>
<td>198</td>
</tr>
<tr>
<td>15  MENTAL ACTIVITY</td>
<td>200</td>
</tr>
<tr>
<td>16  PSYCHOLOGICAL MEASURES</td>
<td>206</td>
</tr>
<tr>
<td>17  SOCIAL FACTORS</td>
<td>216</td>
</tr>
<tr>
<td>18  DEALING WITH STRESS</td>
<td>219</td>
</tr>
<tr>
<td>19  SLEEP</td>
<td>222</td>
</tr>
<tr>
<td>20  DIET</td>
<td>225</td>
</tr>
<tr>
<td>21  MICROBIAL CONSIDERATIONS</td>
<td>246</td>
</tr>
<tr>
<td>22  DENTAL CARE</td>
<td>249</td>
</tr>
<tr>
<td>23  DEALING WITH DOCTORS AND DRUGS</td>
<td>250</td>
</tr>
<tr>
<td>24  HAZARDOUS BEHAVIORS</td>
<td>269</td>
</tr>
<tr>
<td>25  TOXIC EXPOSURES</td>
<td>274</td>
</tr>
</tbody>
</table>
PART III CONCLUSIONS

26 CONSIDERATIONS FOR SOCIETY AND THE FUTURE OF AGING

27 OUR ATTITUDE AND THE OPPORTUNITY OF AGING

Acknowledgments
Glossary
References
Index
LIST OF FIGURES
AND TABLES

Figures
1. Declines in function with aging  page 14
2. Variability increases with age  15
3. Cognitive reserve factor  27
4. The four reserves and Alzheimer’s disease  40
5. Pathways from gut to brain and brain to gut  89
6. Relative odds of Alzheimer’s disease according to APOE genotype and age in Caucasian subjects  175

Tables
1. Changes with aging in the body and brain  5
2. The three goals of aging  7
3. Diseases and processes influenced by the microbiota  129
4. Examples of the influence of the microbiota on the body  130
PREFACE

"Act as if whatever you do makes a difference. It does."
William James (1842–1910), Harvard University psychologist and philosopher, author of Principles of Psychology

Just about everyone wants to know the secret to a long and healthy life. You may think exercise and mental health are key. Both are important, but in fact there are four factors that are central to vibrant living. The key to successful aging is the maintenance of our bodies’ four reserve factors: cognitive, physical, psychological, and social. The status of these reserve factors is a critical component of health and fitness throughout life and is of special importance in aging. Our four reserve factors function to maintain the balance of our body systems, despite the challenges which are encountered. As you will see throughout the book, there are many things we can do to enhance our reserve capacity and preserve our function as we age.

But does it matter what we do? Why should we care? I’d like to tell you why this is important to me, and to you.

As a neurologist, I’ve spent a lifetime studying how the brain works in health and disease and what can be done to enhance brain health with aging. In this book, I’ll reveal what I’ve learned by explaining and demonstrating the importance of the four reserve factors, which are critical to healthy aging. You see, when we’re young, our bodies and brains can handle all sorts of bad behavior, including excessive drinking, lack of sleep, and eating too much junk food. That’s because our young bodies have the reserve capacity to keep us going. But as we age, this capacity diminishes and our resilience suffers unless we carefully cultivate and nurture these four reserve factors.
I will tell you more about this and other essential knowledge in a down-to-earth, readable way that will help you understand your brain, body, and what you can do to keep them perky as you age.

The years of life after the sixth decade should be amongst the happiest of all. This is the time when older persons can enjoy retirement, spend time with family, and devote themselves to special interests, without the need for work. Unfortunately, the quality of these years is often tragically damaged by the neurodegenerative diseases associated with aging: Alzheimer’s disease, Parkinson’s disease, and amyotrophic lateral sclerosis (ALS) (also known as Lou Gehrig’s disease), as well as stroke. As a practicing neurologist for the past 45 years, I have been devoted to taking care of these patients and their families.

The central focus of my efforts in patient care and research is to improve the health of older persons, and to understand why people get these conditions and how they can be prevented. Although our knowledge has improved greatly over these five decades, we still don’t know why most people are affected. I have pursued this work because our knowledge of these diseases is so poor and the ways to help patients are so limited.

For many years, it has been my mission to proclaim the truth that aging is not inevitable – that what we do makes a difference. I have written this book to clarify my positive approach, that there are many things you can do to improve your prospects with aging. The book begins by presenting the scientific basis of these recommendations and then outlines specific actions that will enhance your brain and body as you age. My aim is to help you understand the most important, and the least understood, part of the body: the brain. I will also explain how the brain interacts with the rest of the body and how our response to aging is influenced by our lifestyle choices.
How can we appreciate the work of the brain and its relation with the body? Consider an ordinary day. When I wake up, I am usually aware of what time it is. Somehow, my brain has calculated the approximate time. I notice the relative temperature of the room and move my legs off the bed and onto the floor, which changes my center of gravity so that I can sit up. Regardless of what I am thinking about, my brain calculates what needs to be done on this ordinary morning. The blood flow to my hands and feet is controlled in a dynamic fashion so that I do not lose too much heat. I go to the kitchen and put two pieces of whole wheat bread in the toaster. The movements necessary for this task are quite complex, considering that they involve muscles in the fingers, wrists, forearms, and shoulders. No matter how complicated the movements, I don’t think about them. When the toast pops up, warmed to perfection and crisp, I cover the bread with fig jam, walk to the dining room, sit down, and eat. (Note how both the whole wheat bread and fig jam are both high in fiber, but I am getting ahead of myself.)

At the same time I am waking up and having breakfast, my heart is adapting to the demands made on it, and my liver is delivering glucose to my bloodstream. My liver is also managing the nutrients contained in my breakfast and storing energy as glycogen, and delivering amino acids and other molecules to the rest of my body. My immune system in the gut and elsewhere is monitoring the presence of microbes and microbial products to provide both cellular and antibody defenses against potential pathogens (disease-causing agents). In addition, the microbes in my gut are interacting with my immune system in a way which hopefully limits the development of inflammatory factors that lead to disease. My urinary bladder is monitoring its contents. My brain is busy supervising my blood volume, body temperature, blood pressure, blood sugar,
blood sodium content (all critical to life), and evaluating the need for changes in heart rate, cardiac output, tone of blood vessels, sweating, water intake, excretion, and posture.

Thus, in a few moments of an ordinary morning my brain has made multiple complex calculations regarding my well-being. And other parts of my body have also been busy maintaining my health. We all have the delusion that we are in charge of everything, when actually the most important of human activities are automatic. As humans, all we can do is oversee the intricate interactions that go on between the brain and other parts of our bodies. The unconscious nature of these actions allows us to survive in a world with myriad stimuli which would overburden our consciousness if we needed to pay attention to every task.

These processes involved in waking up are all interrelated: the brain perceives the body, and the body reacts to the brain. There is no part of us which is truly independent, just as there is no person who is truly independent of others. This state of complex interdependence is found from birth throughout life and is the key to healthy aging. The center of this process is the brain. No wonder the Spanish brain scientist Santiago Ramón y Cajal compared the brain’s cerebral cortex to “a garden full of an infinite number of trees.” The neurons comprising Cajal’s trees are vital entities that change according to interactions with the world and with the body. They grow and adapt like trees in a heavy wind. The trees of the cerebral cortex are changed by how we use them and by their relationship to the rest of our bodies.

The French physiologist Claude Bernard (1813–1878) marveled at how the body regulated itself. He coined the term “milieu interieur” to describe the interactions within the body that produced steadiness and health. He said, “the stability of the internal environment (the “milieu interieur”) is the condition for a free and independent life.” Bernard,
who was a friend of Louis Pasteur, recognized the ability of the brain to compensate for external conditions and maintain the balance of body processes “so that its equilibrium results from a continuous and delicate compensation established as if the most sensitive of balances.”

There is a potential danger in Bernard’s use of the metaphor of “balances” applied to the “milieu interieur.” That is, we have a mental image of a balance having two arms, allowing for the weight of one substance or object to be compared with the weight of another. In reality, our internal processes are supremely complex and multifaceted. All of our body parts are interconnected and interdependent (mutually dependent). The balance of our internal structures involves an innumerable number of variables, such as body temperature, blood pressure, heart rate, circulating concentration of red blood cells and electrolytes (such as sodium, potassium, and chloride), and countless others. Moreover, the interactions at the heart of a balanced body are not limited to forces producing increases or decreases in a variable. Frequently, these manipulations involve modulations in which the excitability and other aspects of an organ and its interactions can be adjusted. A healthy, balanced body involves the equilibrium of all body processes, including responses to stress and maintenance of the body’s barriers.

The ability of the body to maintain stability among the interdependent elements we have been discussing is called “homeostasis,” which describes the processes that allow for stability of body functions (Walter Cannon popularized the concept of homeostasis in his book *The Wisdom of the Body*, first published in 1932). The word homeostasis comes from “homeo” (similar to) and “stasis” (standing still). Healthy aging requires us to maintain this stability despite the challenges we all face from the stresses we encounter as we age.

Through millions of years of evolution our bodies have evolved the capacity to precisely monitor and adjust
themselves in response to internal and external conditions. Although the brain is largely responsible for monitoring the balance of the body’s systems, it is heavily dependent on the coordinated functioning of the whole. The brain does not work alone. There are vital interactions of the brain with the circulatory system, gastrointestinal tract, immune responses, and other vital processes. With aging, the quality of these interactions becomes more delicate. The interdependence of our brain with our other organs, as well as the interactions of ourselves with others, is the key to health and fitness with aging.

The interdependence of our brain with our other organs, as well as the interactions of ourselves with others, is the key to health and fitness with aging.

After reading this book, you’ll better understand the interactions of the brain, body, physical environment, and society that determine health, disease, fitness, and longevity. The wonderful part of this discussion is that it can lead to actions that enhance quality of life, avoid disease, enhance fitness, and provide meaning with aging.

A chief reason these interactions are not recognized for their critical nature is that the reserve capacity in early life is so high. Young people are very well made and are resilient to damage from unhealthy behaviors. They can often suffer partial losses in function without apparent effect. Because of evolution, young people are frequently able to have poor lifestyle habits which do not notably impact their health. With age, our reserve capacity is reduced and the interdependent interactions we are about to discuss become critical and vital to health and fitness. The concept of reserve capacity comes from the idea of military forces which are “withheld from action to serve as
later reinforcements” (OED online). The reserves are ready for activity and available to serve when needed. Similarly, our reserve factors allow us to have resilient responses to challenges which occur in our lives.

The key words here are attention and attitude. As I continue my breakfast, what further dietary choices will I make? Will I be involved in cognitive and physical tasks on this ordinary day? Attention to the role that daily lifestyle choices have in health and fitness is necessary throughout life, and especially important in aging. Will my attitude toward aging be negative, considering it to be uniformly negative? Or will I appreciate the truth that aging is an opportunity to be welcomed with gratitude?

Our recognition of the miracle of our life and function is dependent upon the attitude we have in regard to our survival, and our ability to appreciate the opportunities of aging. What we do makes a difference. This book presents detailed advice about what each one of us can do to enhance our experience of aging. Even though we cannot stop all age-related declines in function, we can delay their onset and reduce their impact on our lives.

Robert P. Friedland, M.D.
Louisville, Kentucky