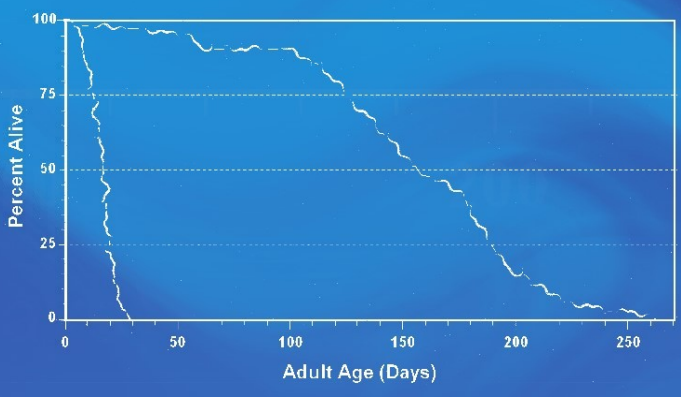
Gregory M. Fahy *Editor-in-Chief*

Michael D. West · L. Stephen Coles
Steven B. Harris *Associate Editors*

The Future of Aging

Pathways to Human Life Extension



Springer

The Future of Aging

Gregory M. Fahy · Michael D. West ·
L. Stephen Coles · Steven B. Harris
Editors

The Future of Aging

Pathways to Human Life Extension

Springer

Editors
Gregory M. Fahy
Intervene Biomedical, LLC
Box 478
Norco CA 92860
USA
intervene@sbcglobal.net

Dr. Michael D. West
BioTime, Inc.
1301 Harbor Bay Parkway
Alameda CA 94502
USA
mwest@biotimemail.com

L. Stephen Coles
Institute of Molecular Biology
Department of Chemistry and Biochemistry
Young Hall
University of California
Los Angeles
CA 90095-1569
USA
scoles@ucla.edu

Steven B. Harris
Critical Care Research, Inc.
10743 Civic Center Drive
Rancho Cucamonga CA
91730
USA
sbharris1@earthlink.net

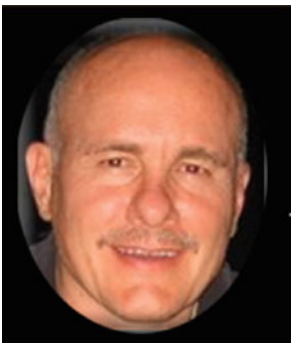
ISBN 978-90-481-3998-9 e-ISBN 978-90-481-3999-6
DOI 10.1007/978-90-481-3999-6
Springer Dordrecht Heidelberg London New York

Library of Congress Control Number: 2010927444

Cover illustration: On the cover: The small nematode worm, *C. elegans* (wavy lines), can realize some very large gains in lifespan. Compared to the standard N2DRM (wild-type) worm, worms with a strong mutation in a single gene (the *age-1 (mg44)* allele) can live 10 times longer, and can do so in excellent health. This striking result brings into question the very nature of aging, and raises the possibility of someday extending the lifespans of humans in good health as well. The latter subject is the theme taken up in this book.

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)



This book is dedicated to the fond memory of Christopher B. Heward, Ph.D., a tireless and dedicated clinical biogerontologist and a superb laboratory scientist who worked at the interface of business and biomedicine as the President of the Kronos Science Laboratories, where he conceived and pursued a variety of research and development projects aimed variously at early detection and prevention of age-related diseases and understanding and slowing the aging process in patients. He was internationally recognized as a seminal thinker in the area of biological aging and was the author and co-author of numerous scientific articles and book chapters. He was a consummately skeptical enthusiast for interventive gerontology.

It is an extreme and tragic irony that Chris developed cancer at a relatively young age and died on January 10, 2009 after a vigorous 3-month battle. He set a magnificent example of how to live life courageously to the fullest without illusion. He will be sorely missed by all who knew him.

Preface

Biogerontology is coming of age. It now seems clear that a fundamental understanding of the molecular pathways underlying age-related pathology has the potential to translate into a net economic impact of over a trillion dollars a year in the US alone and to alleviate a massive toll of human suffering. At the same time, a tidal wave of aging post World War II baby boomers is poised to begin flooding the shores of our health care system within the coming decade. It is therefore now strategic and timely for medical research to turn its attention to the molecular and cellular mechanisms of aging and age-related disease, and the purpose of this book is to provide a broad perspective on future possibilities for mitigating aging and improving the human condition that can be envisioned today based on available knowledge and reasonable deduction.

One of the largest barriers to successful intervention in aging is likely psychological rather than technological. A widespread misperception persists that modifying human aging borders on the impossible. However, this skepticism is not supported by science. There are now numerous examples of therapies based on fundamental insights in molecular biogerontology that are in clinical development, and many more such therapies are expected to unfold over time scales ranging from the very near term to the more distant future. We call attention to many of these in this volume.

Without a doubt, there has never been a more exciting time in the history of biogerontology than the present and, just as certainly, the best is yet to come. Ten years ago, Leonard Guarente and Cynthia Kenyon expressed their growing sense of hope and optimism about the future of biogerontology in these inspiring words in an outstanding article in *Nature* (Guarente and Kenyon 2000):

> The field of ageing research has been completely transformed in the past decade. . . . When single genes are changed, animals that should be old stay young. In humans, these mutants would be analogous to a ninety year old who looks and feels forty-five. On this basis we begin to think of ageing as a disease that can be cured, or at least postponed. . . . The field of ageing is beginning to explode, because so many are so excited about the prospect of searching for – and finding – the causes of ageing, and maybe even the fountain of youth itself.

But the results that stimulated such hope in 2000 have been far surpassed in the last ten years. To give just one example, the seminal observation in the 1980s that

genetic damage (the *age-1* mutation) in *C. elegans* could extend lifespan by 40–65% (Klass 1983; Johnson 1987; Friedman and Johnson 1988), which ultimately led to the modern paradigm of genetic regulation of aging, was confirmed but on a practical level dwarfed in 2007 by the discovery that stronger mutations in the same *age-1* gene can actually extend lifespan in *C. elegans* by a staggering 10-fold (Ayyadevara et al. 2008; Shmookler Reis and McEwen 2010). The finding that a genetic hierarchy controlled by one gene can in effect control 100% of the normal aging process for a time in excess of the normal maximum lifespan in at least this species is a profound development that we celebrate on the cover of the present volume as symbolic of the future potential of interventive gerontology. Nor have results with higher organisms failed to excite the interest of biogerontologists, the public, and the business community as well. The recent large investment in biogerontology by a major pharmaceutical company marks a new era of promise for intervention into human aging.

Despite all of the progress of the past decade of biogerontological research, unanimity of views on the meaning and implications of present knowledge has not yet been achieved. Different interpretations of and hypotheses about aging are still possible, and controversy continues even over the meaning of specific animal and cellular models and their eventual applicability or lack of applicability to or implications for human intervention. Accordingly, the reader will notice basic differences of opinion between some of the contributors to this book. This is as it should be, and it is hoped that some of these disagreements will be stimulating. In fact, we may be justifiably accused of deliberately stoking the fires of disagreement in some cases in the interests of promoting debate and thereby accelerating the resolution of conflicting views and stimulating new thoughts in general.

Despite some present disagreements, however, the more important truth is that modern biogerontology has developed many commonly-agreed upon broad themes that seem sufficiently reliable to justify an examination of their implications for the future of human aging, and such an examination now seems particularly timely.

Although this book is entitled "*The* Future of Aging," no one can predict *the* future in specific detail, and we do not attempt to do this here. Instead, our goal is only to provide a broader and more complete and practical sense of what the future might bring than has been available in one place heretofore.

Part One of this volume considers historical, anthropological, philosophical, ethical, evolutionary, and general evidentiary perspectives on the proposal that aging in the future may be appreciably different from aging as it is experienced today. Given often-repeated skepticism that aging either can or should be significantly modified in man, the arguments in Part One should help to establish the contrary view that aging intervention ought to be both generally feasible and desirable.

Part Two presents many specific and potentially transformative proposed interventive approaches, organized in roughly chronological order, with the earliest interventions coming first and the more distant interventions coming last. One can imagine useful interventions proceeding in a series of steps, many of which seem likely to be steps outlined in this book. The possible steps described here begin to provide a kind of tentative roadmap to the future of potential pathways to human life extension in which greater and greater control over aging is achieved over the

next several decades. But it seems unlikely we will have to wait decades for major changes to become evident. In fact, in trying to decide on the sequence of chapters in Part Two, it was striking how many of these chapters, while offering powerful and paradigm-changing potential interventions, are also vying to be among the first to have their approach put into practice. And yet even as impressive as the current list of interventive approaches is, the rapid pace of ongoing developments in biogerontology ensures that the list is incomplete, a fact that underscores even more the potential that lies ahead.

It is hoped that the present glimpse into the future of human aging and the refinements to it that will follow will be of assistance to policy makers as they attempt to decide how public funds should be directed and how population aging should be addressed. Governmental projections of future human life expectancy have been consistently and significantly in error in failing to anticipate steady and even accelerating reductions in mortality rates (Horiuchi 2000; Tuljapurkar et al. 2000; Vaupel 2010), perhaps in part because of the lack of an adequately convincing argument for or any sufficiently concrete therapeutic basis for a timetable for greater future longevity. In addition, current NIH spending priorities continue to ignore the fact that learning how to successfully mitigate aging itself would be a dramatically more efficient and therefore more humane way to deal with the diseases of aging, which account for the bulk of US health care expenditures, than continuing to devote such an overwhelming share of our research resources to a piecemeal attack on these diseases. Although this point has been made many times before, perhaps the availability of a credible roadmap to a better future for aging will make the argument easier for policy makers to accept in the future.

In the end, the extent to which aging can be modified will impact all of us and our loved ones in a very personal way. This bald fact alone justifies bringing together thought leaders in the field of aging research to attempt to glimpse the future even if we are at a time in history when the full function of the human genome is not known and our present knowledge of aging remains very incomplete. Fortunately, despite the acknowledged limitations of today's knowledge, today's evidence already speaks for itself. We truly and unquestionably are learning how to intervene, in diverse ways, into aging, and it seems inevitable that this will materially affect human aging. The future of aging will begin to arrive sooner than many of us think.

We thank the editorial staff at Springer, and particularly Fabio de Castro, Marlies Vlot, and Tanja van Gaans, for their trust and for their steadfast support of our concept for this book, even in the face of some strong opposition by certain reviewers. We thank as well all of the anonymous reviewers of the concept of this book, whose comments both pro and con helped us to refine our message. We also thank Brenda Peters for her devoted, highly skillful, cheerful, and very helpful volunteer editorial assistance, and Karen Jessie of Integra India for outstanding and understanding production assistance.

Finally, we thank our many wonderful authors, who cheerfully and patiently endured an at times rather vigorous process of peer review. Their opinions, of course, remain their own!

References

Ayyadevara S, Alla R, Thaden JJ, Shmookler Reis RJ (2008) Remarkable longevity and stress resistance of nematode PI3K-null mutants. Aging Cell 7:13–22

Friedman DB, Johnson T (1988) Three mutants that extend both mean and maximum life span of the nematode, Caenorhabditis elegans, define the age-1 gene. J Gerontol 43:B102–B109

Guarente L, Kenyon C (2000) Genetic pathways that regulate ageing in model organisms. Nature 408:255–262

Horiuchi S (2000) Greater lifetime expectations. Nature 405:744–745

Johnson T (1987) Aging can be genetically dissected into component processes using long-lived lines of Caenorhabditis elegans. Proc Natl Acad Sci 84:3777–3781

Klass MR (1983) A method for the isolation of longevity mutants in the nematode Caenorhabditis elegans and initial results. Mech Ageing Develop 22:279–286

Shmookler Reis RJ, McEwan JE (2010) Methuselah's DNA: defining genes that can extend longevity. In: Fahy GM, West M, Coles LS, Harris SB (eds) The Future of Aging: Pathways to Human Life Extension. Springer, Berlin Heidelberg New York (in press)

Tuljapurkar S, Li N, Boe C (2000) A universal pattern of mortality decline in the G7 countries. Nature 405:789–792

Vaupel JW (2010) Biodemography of human ageing. Nature 464:536–542

California, USA

Gregory M. Fahy
Michael D. West
L. Stephen Coles
Steven B. Harris

Contents

Contributors

Francisco J. Alcaín Departamentode Biología Celular, Fisiología e Inmunología, Facultad de Ciencias, Campus Universitario de Rabanales, Edificio Severo Ochoa, Universidad de Córdoba, 14014-Córdoba, Spain, bc1altef/@uco.es

Richard Aspinall Cranfield Health, Vincent Building, Cranfield University, Cranfield, Bedfordshire, MK43 0AL, UK, r.aspinall@cranfield.ac.uk

Anthony Atala Wake Forest Institute for Regenerative Medicine, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157, USA, aatala@wfubmc.edu

Abraham Aviv The Center of Human Development and Aging, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark, NJ, USA, avivab@umdnj.edu

John D. Bogden Department of Preventive Medicine and Community Health, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark, NJ, USA, bogden@umdnj.edu

L. Stephen Coles Institute of Molecular Biology, Department of Chemistry and Biochemistry, Young Hall, University of California, Los Angeles, CA 90095-1569, USA, scoles@ucla.edu

Zheng Cui Section of Tumor Biology, Department of Pathology, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA, zheng.cui@gmail.com

Morgan Carlson Department of Bioengineering, University of California, Berkeley, CA 94720, USA, morgancarlson@gmail.com

Irina M. Conboy Irina Conboy, B108B Stanley Hall, Department of Bioengineering, UC Berkeley, Berkeley, CA 94720-1762, USA, iconboy@berkeley.edu

Rafael de Cabo Laboratory of Experimental, Gerontology, National Institute on Aging, NIH, Baltimore, MD 21224, USA, decabora@mail.nih.gov

Aubrey D.N.J. de Grey SENS Foundation, PO Box 304, El Granada, CA 94018, USA, aubrey@sens.org

Gregory M. Fahy Intervene Biomedical LLC, Box 478, Norco, CA 92860, USA, intervene@sbcglobal.net

Robert A. Freitas Jr. The Institute for Molecular Manufacturing, Palo Alto, CA, USA, rfreitas@rfreitas.com

John D. Furber Legendary Pharmaceuticals, PO Box 14200, Gainesville, FL 32604, USA, johnfurber@LegendaryPharma.com

Lee F. Greer Genescient, LLC, Irvine, CA, USA, lgreer@genescient.com

Terry Grossman Frontier Medical Institute, Denver, CO, USA, terry.grossman@comcast.net

Christopher B. Heward[†] Kronos Science Laboratory, Phoenix, AZ 85018, USA

Steven Horrobin College of Medicine, University of Edinburgh, Edinburgh, Scotland, s_horrobin@hotmail.com

David Kekich Maximum Life Foundation, Huntington Beach, CA 92648, USA, kekich@maxlife.org

Betsy T. Kren Department of Medicine, University of Minnesota Medical School, 420 Delaware Street SE, MMC 36, Minneapolis, MN, USA, krenx001@umn.edu

Ray Kurzweil Kurzweil Technologies, Inc., Wellesley, MA, USA, ray@kurzweiltech.com

Anthony D. Long Genescient, LLC, Irvine, CA, USA, along@genescient.com

Kennedy C. Matsagas Genescient, LLC, Irvine, CA, USA, kmatsagas@genescient.com

Joan E. McEwen Department of Geriatrics, University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA, McEwenJoanE@uams.edu

Robin K. Minor Laboratory of Experimental Gerontology, National Institute on Aging, NIH, Baltimore, MD 21224, USA, minorro@mail.nih.gov

Wayne Mitchell Cranfield University, Cranfield Health, Vincent Building, Cranfield, Bedfordshire, MK43 0AL, UK, w.mitchell@cranfield.ac.uk

Joshua Mitteldorf Department of Ecology and Evolutionary Biology, University of Arizona, Tucson, AZ 85720, USA, josh@mathforum.org

Laurence D. Mueller Genescient, LLC, Irvine, CA, USA, lmueller@genescient.com

[†]Deceased

Courtney Everts Mykytyn Highland Park, 5657 Fallston Street, CA 90042, USA, cemykytyn@gmail.com

Kaveh Navab David Geffen School of Medicine, UCLA, Los Angeles, CA 90095, USA, KNavab@ucla.edu

Mohamad Navab Department of Cardiology, UCLA Medical Center, 10833 Le Conte Ave., Los Angeles, CA 90095, USA, MNavab@mednet.ucla.edu

Francisco R. Portell Gencia, Inc., Charlottesville, VA, USA, francisco@genciabiotech.com

Michael Rae SENS Foundation, 1230 Bordeaux Drive, Sunnyvale, CA 94089, USA, michael.rae@sens.org

Cristina L. Rizza Genescient, LLC, Irvine, CA, USA, crizza@genescient.com

Michael R. Rose Genescient, LLC, Irvine, CA, USA, mrose@genescient.com

Robert J. Shmookler Reis Department of Geriatrics, University of Arkansas for Medical Sciences, and Research Service, Central Arkansas Veterans Healthcare System, Little Rock, AR 72205, USA, rjsr@uams.edu

Rafal Smigrodzki Gencia, Inc., Charlottesville, VA, USA, rafal@genciabiotech.com

Stephen R. Spindler Department of Biochemistry, University of California, Riverside, CA 92521, USA, spindler@ucr.edu

Clifford J. Steer Department of Medicine, University of Minnesota Medical School, VFW Cancer Research Center, 406 Harvard Street SE, Minneapolis, MN, USA, steer001@umn.edu

José M. Villalba Departamento de Biología Celular, Fisiología e Inmunología, Facultad de Ciencias, Universidad de Córdoba, 14014- Córdoba, Spain, bc1vimoj@uco.es

Bryant Villeponteau Genescient, LLC, Irvine, CA, USA, bvilleponteau@genescient.com

Michael D. West CEO, BioTime, Inc. and Embryome Sciences, Inc., Alameda, CA, USA, mwest@biotimemail.com

Roger Yu Hospital Medicine Program, Beth Israel Deaconess Medical Center, 330 Brookline Ave, Span 2, Boston, MA 02215, USA, RogerYu.MD@gmail.com

Part I
Introduction and Orientation

Chapter 1
Bridges to Life

Ray Kurzweil and Terry Grossman

Contents

1.1 Introduction

In two recent books (Kurzweil and Grossman 2004, 2009), we have previously presented an optimistic exploration of medical knowledge and tools that give readers a powerful opportunity to greatly improve their health. In a snapshot in time of today's medicine and tomorrow's potential, we showed that improving your health today will have long-lasting positive effects and make it more likely for you to benefit from the more powerful medical tools of the future.

R. Kurzweil (✉)
Kurzweil Technologies, Inc., Wellesley, MA, USA
e-mail: ray@kurzweiltech.com

G.M. Fahy et al. (eds.), *The Future of Aging*, DOI 10.1007/978-90-481-3999-6_1,

Employing a "bridge" metaphor, what we call the first bridge of present-day therapies and guidance should enable many people to remain healthy long enough to take full advantage of the second bridge – the Biotechnology Revolution, which is providing us with the means to reprogram the outdated software that underlies our biology. As we learn the genetic and protein codes of our biology, we are gaining the means of turning off disease and aging while we turn on our full human potential. This second bridge, in turn, will lead to the third bridge – the Nanotechnology-AI (Artificial Intelligence) revolution. This revolution will enable us to rebuild our bodies and brains at the molecular level. In the present chapter, we briefly summarize this overview of the future of aging to provide a general context for the rest of this book.

1.2 Bridge One

Bridge one is what you can do right now to slow down aging and disease processes in order to increase your chances of remaining healthy until later bridges become manifest. We are only about 15 years from the maturation of the second bridge, and about 20–25 years from the full realization of the third bridge. It is theoretically quite feasible, therefore, even for baby boomers to remain in good health until we get to the "tipping point" in life extension. Keep in mind that bridge one is a moving frontier: our knowledge of how to stay healthy and vital is rapidly accumulating. As our knowledge increases, bridge one will essentially morph into bridge two.

The best proven method of increasing lifespan across a broad range of animal species is caloric restriction. So, let's begin by looking at modified caloric restriction as one of the cornerstones of our bridge one therapies and then have a brief look at other suggestions for heading off aging changes. By following these simple suggestions, it is our goal to help individuals live long enough and remain in good health long enough to take full advantage of the more powerful bridge two and three technologies that will lead to more profound increases in human longevity in the decades ahead.

1.2.1 Caloric Restriction

Caloric Restriction (CR) involves eating less food while still maintaining adequate nutrition. As such, CR is different from starvation or famine. CR is scientifically the best-demonstrated intervention to safely increase longevity across a broad variety of species, including C. elegans, Drosophila, and mice, and to be tested for this effect in monkeys. Compared with controls eating ad libitum, CR animals have been shown to increase their average life expectancy as well as their maximum lifespan. More than 2,000 animal studies show dramatic results across many different species (Lane et al. 2002). Consequently, we have good evidence that restricting calories slows down aging and can extend youthfulness. These experiments have

not yet shown life extension in humans, but studies of humans practicing CR have shown reduction in disease and aging biomarkers similar to those seen in animal studies (Hursting et al. 2003). Free radicals cause a gradual deterioration of body tissues, particularly fragile cell membranes, or a stiffening of collagen proteins by cross-linkage, in both animals and humans, and biogerontologists attribute multiple processes associated with aging to the effects of free radical damage (Ferrari and Torres 2003). CR animals have significantly lower levels of free radicals, so they also have less free-radical damage to their cell membranes. Levels of liver enzymes that detoxify free radicals are also about 60 percent higher in low-calorie animals (Koizumi et al. 1987).

CR animals have more robust DNA-repairing enzymes. Random point mutations in DNA can lead to cancer and can accelerate other aging processes, so more effective DNA-repair enzymes would help explain the slower aging and lower rate of tumors in these animals (Licastro et al. 1988).

Of course, there is a limit to the degree to which CR can be done in an attempt to extend life. All CR animals eventually die. Because of the need to obtain adequate nutrients, it is not possible to reduce calories to one-third of normal levels and expect animals to live three times as long. It appears that, at least in the case of mammals such as rats, the optimal level of CR for longevity is about two-thirds of the calories that the animals would consume if they were eating ad libitum.

1.2.1.1 CR in Humans

A number of studies have demonstrated the potential benefit of CR for humans. For example, the people living in the Okinawa region of Japan have 40 times the number of centenarians compared with the Japanese mainland, and they experience very little serious disease before age 60 (Facchini et al. 1989; Kahn 1990). Okinawans who follow the traditional ways remain active much longer than their peers in other areas of Japan. The key difference seems to be their lower caloric intake. Extrapolating animal studies to humans, some researchers have estimated that our maximum lifespan might be extended from 120 to 180 years (Angier 1990). Yet very few of us live to 120 as it is, and others' extrapolations have been far less optimistic. The truth is that the true quantitative benefits of CR for life extension in humans are simply unknown, but we certainly know that restricting calories can improve human health and reduce many risk factors for life-limiting diseases in people. For a detailed analysis of the effects and potential benefits of CR, see Chapter 12.

The benefits of CR, whatever they may be, will apply only to your remaining life expectancy. If you are now 40 and have a remaining life expectancy of, say, 40 years, CR will only apply to that remaining period if you have not begun a CR program already. Therefore, in theory, the earlier you start CR, the greater the benefits. However, regardless of when you start, you'll achieve the health benefits of maintaining a lower weight.

One of the biggest problems of using CR for human life extension, of course, is that it isn't pleasant. But Dr. C. Ronald Kahn, Executive Director of the Joslin Diabetes Center at Harvard Medical School, and his colleagues have created a

mouse model that seems to enjoy at least some of the benefits of CR without requiring CR itself. These FIRKO (Fat-specific Insulin Receptor Knock Out) mice have been genetically modified such that they lack a single gene that controls insulin's ability to allow adipocytes to store fat (Blüher et al. 2003). FIRKO mice can eat considerably more than normal mice – as much as they want – yet have 50–70 percent less body fat. They appear resistant to diabetes and remain healthier far later in life than control animals, and can live 18 percent longer. Both FIRKO mice and CR animals have significantly lower blood glucose levels (Cerami 1985), which may reduce non-enzymatic glycation reactions (for more details about the latter, see Chapter 19). Fortunately, many companies are now pursuing drugs that can block the fat insulin receptor and hopefully allow humans to gain benefits similar to those of FIRKO mice, without CR.

For now, we suggest a moderate form of CR, not as austere as the 35 percent reduction typically used in animal experiments. In Okinawa, it is customary to recite "hara hachi bu" (stomach 80 percent full) before eating. In other words, the Okinawans try to restrict calories about 20 percent, and this has translated into the longest life expectancy in the world.

We suggest the following guidelines:

Eat 20 percent fewer calories. A 140 pound sedentary woman should eat approximately 1,800 calories daily to maintain her weight. Hara hachi bu would mean eating 1,440 calories – and would lead to a weight loss of about 25 pounds (Kurzweil and Grossman 2004). A 180 pound moderately active man needs 2,700 calories to remain at the same weight. Reducing this by 20 percent would correspond to 2,160 calories per day – and gradually lead to a 35 pound weight loss.

Select foods low in caloric density. For example, choose oranges instead of orange juice. Another way to reduce calories is to eat low-starch vegetables such as broccoli and summer squash, which are filling and have relatively few calories, instead of potatoes or rice.

Focus on fiber. Another choice is foods rich in fiber, which provides bulk and texture with no digestible calories. Fiber also has health benefits by lowering cholesterol levels, improving regularity, and reducing the risks of colon cancer. Most vegetables are, of course, high in fiber. There are also many foods designed to be carbohydrate substitutes that use fiber (as well as vegetable protein) to replace the bulk and texture of starch, such as low-carbohydrate cereals and breads.

Consider calorie blockers. Another strategy for weight loss is to block the digestion of some of the food that you eat. There are some limited but promising approaches to doing this with carbohydrate and fat blockers.

Starch blockers. Precose is a prescription starch blocker taken with meals. It is mostly used in the treatment of diabetes, but delays starch absorption. There are a number of "starch blockers" available over-the-counter; however, we have had mixed results with these products in our own informal tests, which suggest that Precose may prove more effective than nonprescription starch blockers.

Fat blockers. Orlistat, available by prescription as Xenical or over-the-counter as Alli, blocks lipases. Orlistat is said to block up to one-third of fat calories. (Harrison et al. 2003). Keep in mind that key nutritional supplements are fat based

(for example, EPA/DHA), so do not take fat blockers within an hour of taking oil based supplements.

More effective calorie blockers, as well as body-fat inhibitors, are in the pipeline. In the meantime, there are extensive benefits to restricting calories and maintaining a lower body weight.

A combination of moderate CR along with a diet that avoids high-glycemic-load foods (that is, foods high in simple sugars and starches) and that is generally low in fat, while emphasizing healthy fats (for example, fish oil, nuts, and the monounsaturated fat found in extra virgin olive oil) can allow you to still eat plenty of food – and therefore never be hungry.

Recent research has identified certain substances to be caloric restriction mimetics, that is, they produce at least some of the biochemical changes created by reducing calories. One CR mimetic is the prescription drug metformin, which reduces early stage insulin resistance, mimics the gene expression changes induced by CR, and extends lifespan in animals (Dhahbi et al. 2005). Another seems to be resveratrol, which is found in red wine. Mice that were fed significant amounts of resveratrol along with a high-fat diet lived as long as mice fed a normal-fat diet and were protected from the negative health consequences of the calories and fat of the high fat diet (Baur et al. 2006). You would need to supplement with about 400–700 mg a day of resveratrol to match the supplementation of these mice, but certain variations of resveratrol may be effective at much lower doses (Barger et al. 2008). For more information about the effects of resveratrol and the sirtuin pathways and their relationship to calorie restriction, see Chapter 10.

1.2.2 Exercise

Evidence from the medical literature suggests that both aerobic and resistance (strength) training exercise are associated with substantial health benefits (McGinnis and Foege 1993). All major progressive diseases such as heart disease, stroke, and type 2 diabetes are dramatically reduced with regular exercise. Our ancestors spent their lives as hunter-gatherers only a few dozen centuries ago, living a lifestyle that entailed plenty of exercise, and part of the modern epidemic of degenerative disease results from our modern-day sedentary lifestyles.

1.2.2.1 The Remarkable Benefits of Exercise

In an 8-year study published in the Journal of the American Medical Association researchers divided 13,344 participants into five fitness categories according to their exercise habits, ranging from sedentary (no regular exercise program) to high fitness (walking or running 20–30 miles per week or more). Overall death rates for the people in the moderate exercise group were 60 percent less than those of the sedentary group and there was even more benefit for the high-fitness category, particularly with respect to cardiovascular disease (Blair et al. 1989).

Despite this proven value of exercise, 72 percent of American women and 64 percent of American men do not participate in any regular physical activity. Yet it does not require a considerable expenditure of time to reap benefits. A Harvard Medical School study showed that as little as 30 minutes per day can provide significant benefit (Lee 2003).

An effective exercise program should include three forms of training: aerobic exercise, resistance training and stretching.

1.2.2.2 Aerobic Exercise

Aerobic exercise such as walking, swimming, cycling, jogging or cross-country skiing significantly lowers the risk of cardiovascular disease, cancer, and other diseases. It also provides immediate benefits such as weight loss, lower blood pressure, better sleep and mood and improved cholesterol profile (Liem et al. 2003).

An effective aerobic exercise session requires continuous, rhythmic use of the large muscles for at least 20 minutes. According to the American College of Sports Medicine (ACSM), during aerobic exercise, the goal is to keep your heart rate between 60 and 80 percent of your maximum predicted heart rate, which you can estimate as 220 minus your age [(www.acsm.org/health+fitness/pdf/fitsociety/fitsc103.pdf), p. 5].

The four phases of aerobic exercise are:

1. Warmup. Begin to warm your muscles by walking at an easy pace, about 3 miles per hour, for a few minutes.
2. Aerobic exercise. The majority of your exercise routine is the aerobic phase, in which you exercise vigorously enough to bring your heart rate into your training range. Sessions should last at least 20 minutes – and preferably 30 minutes or more – to get a training effect on your heart.
3. Cool down. Cool down by again by walking about 3 miles per hour for a few minutes. This allows your heart rate to return to normal gradually and prevents pooling of blood in your legs and feet, which can lead to lightheadedness or syncope.
4. Recovery (stretching). Muscles, tendons and ligaments tend to tighten after exercise, so it is important to lengthen these tissues by gentle stretching at the end of each session.

1.2.2.3 Resistance (Strength) Exercise

Resistance or strength training consists of exercises designed to increase strength and muscular endurance. You can use free weights, weight machines or specially designed rubber bands. For many people, rubber bands are an optimal choice with which to begin. Strength training with bands has many advantages: it is easy to learn; bands are inexpensive; they can be used at home; and they are lightweight and simple to carry with you when traveling. Free weights, on the other hand, require

proper lifting technique and balance to avoid injury and to train the correct muscles. Weight machines are easier to use, but often require that you go to a gym.

The older you are, the more important it is to perform regular strength training. Sedentary individuals can lose up to 10 percent of their lean muscle mass each decade after 30 years of age, and the loss accelerates after 60 (Deschenes 2004).

The following tips should be helpful:

- Work out 2–3 times a week on non-consecutive days.
- Always exhale during the exertion phase of each exercise.
- Perform at least one set of exercises on each major muscle group.
- First work the large muscle groups, such as the chest and back, and then the smaller muscles, such as the biceps.
- Use slow, careful, controlled movements.
- Do 8–12 repetitions per set.
- Vary your program and increase either weights or thickness of bands as you progress.

1.2.2.4 Stretching

Stretching increases the range of motion in your joints. Muscles, tendons, and ligaments tend to shorten either as a result of aging or after exercise. Flexibility training or stretching helps to slow down that process. The American College of Sports Medicine (ACSM) identifies many other benefits to flexibility training, including better physical performance, better circulation, improved posture, stress relief, and enhanced coordination and balance (American College of Sports Medicine 2010). In addition, stretching may help to prevent aging of the extracellular matrix (see Chapter 19).

According to the ACSM guidelines (ACSM Fit Society Page, Spring 2002, "Enhancing your flexibility," p. 5), the following procedures should be followed.

Warm up first to make the muscles supple and easier to stretch.
Focus on the major muscle groups (front and back of the legs, shoulders, chest, etc.).
Perform the stretches at least three times a week.
Stretch muscles slowly until you feel a slight pull, not pain.
Hold each stretch for 10–30 seconds. Don't bounce.
Start slowly and work up.

1.2.3 Nutritional Supplementation

Many people believe that with good diet, vitamin and mineral supplementation is unnecessary. However, numerous factors contribute to a scenario in which most adults need supplementation. Current farming methods are associated with lower

levels of the vitamin and mineral content in fruits and vegetables, and almost no one eats enough fresh produce to get adequate amounts of these nutrients without supplementation. Digestive function also decreases with age so that nutrient absorption and assimilation is reduced. By taking a daily multiple vitamin mix, the body can use what it needs and simply discard the rest.

In addition, some new research suggests that many people have genetic defects that can only be corrected by taking appropriate nutritional supplementation. Bruce Ames at the University of California, Berkeley has demonstrated at least 50 genetic diseases that involve defective vitamin-cofactor binding sites that can be corrected by nutritional supplementation (Ames et al. 2002). Some of these are very common and altogether affect over a billion people. As one example, methylenetetrahydrofolate reductase (MTHFR) is the enzyme that turns folic acid into its active form and helps convert homocysteine back to methionine. Up to 20 percent of people in the Caucasian and Asian populations have MTHFR polymorphisms and require much more folic acid than the RDA of 400 micrograms per day for optimal methylation. For people that carry this polymorphism, taking the RDA amount is rarely adequate to control abnormal methylation, a major cause of many serious diseases and accelerated aging (Botto and Yang 2000; Ames et al. 2002).

It is estimated that even in developed countries, much of the population consumes less than the RDA amount of one or more vitamins. In the underdeveloped world, the situation is often critical, involving multiple deficiencies. But the consequences of lacking even one nutrient can be quite serious. Deficiencies of vitamins C, B6, B12, folic acid, and the minerals iron and zinc, for example, lead to DNA damage and can cause cancer (Ames and Wakimoto 2002).

Taking nutritional supplements makes economic sense as well. A study commissioned by Wyeth Consumer Healthcare showed if all Americans over age 65 were to take a multiple vitamin daily, Medicare would save an estimated $1.6 billion over 5 years because of the resulting decrease in healthcare expenditures (Dobson et al. 2004).

Finally, silent inflammation has been increasingly found to be a factor predisposing to many serious chronic diseases. The results of a double-blind, placebo-controlled study published in the American Journal of Medicine showed that silent inflammation decreased by one-third when patients took a daily multiple vitamin (Church et al. 2003).

1.2.3.1 Basic Supplement Recommendations

The two supplements that we feel should be taken by virtually everyone over 30 are a multiple vitamin/mineral formulation and fish oil. For the former, we suggest a daily multiple vitamin formula that contains enough vitamins and minerals to meet the needs of optimal nutrition. These amounts are sometimes greater than the RDA amounts, which are primarily intended to prevent deficiency diseases like scurvy and rickets. Typically, a one-a-day daily multiple vitamin pill won't suffice, and you'll need to take a daily regimen that typically has 2–6 pills per day. This will allow each tablet or capsule to be of a comfortable size for you to swallow. It is not acceptable

to take 2–6 one-a-day vitamins either. Doing so would lead to your getting excessive amounts of one vitamin or mineral and perhaps not enough of another.

In addition to eating fish several times each week, it is helpful to take supplemental fish oil, which is a rich source of the omega-3 fatty acids eicosapentanenoic acid (EPA) and docosahexaenoic acid (DHA). EPA and DHA are precursors to anti-inflammatory eicosanoids in the body that help reduce silent inflammation.

Several medical authorities have come out in support of fish oil supplementation in certain cases (Kris-Etherton et al. 2002). The American Heart Association recommends one gram of fish oil daily for patients with coronary artery disease (Kris-Etherton et al. 2002) The National Institutes of Health (NIH) considers fish oil of value in the treatment of heart patients as well, and also feels it has value in the treatment of elevated triglycerides and high blood pressure (http://www.nlm.nih.gov/medlineplus/druginfo/natural/patient-fishoil.html). There is no RDA for omega-3 fats, but NIH recommends four grams a day for healthy adults. Vegetarians can get 2.5 g of omega-3 fats from each teaspoon of flaxseed oil.

1.2.4 Benefiting from Predictive Genomics

Uncovering your personal health risks, largely hidden until now within your genes, will enable you to formulate a preventive health program that is specific to you (see also Chapter 7, by Heward). The current consensus is that there are in the vicinity of 23 thousand human genes. Your ability to obtain solid information about these has just begun, but it will increase exponentially over the next few years. Modern genomic analysis can now accomplish in minutes what once took weeks of testing. As a result, the one-size-fits-all type of medicine that physicians have been practicing will soon be replaced by individualized therapies. This will enable you to create the perfect bridge one program for yourself: a diet and exercise plan as well as nutritional supplements and prescription drugs personalized for your genome.

Predictive genomics remains a relatively new bridge one diagnostic tool, but there are already a number of commercially available genomics tests to help predict your predisposition to many serious, but preventable or modifiable, diseases, such as heart disease, Alzheimer's, or cancer. When doing genomics testing, it is important to remember that, for most genes tested, your genes merely express tendencies. Your lifestyle choices have a much larger role in determining what happens, or how your genes are expressed.

Genomics tells you your tendencies, and therapies that will be able to alter these tendencies are still in their infancy, which is another reason it is important for you to remain as healthy as possible for the next decade or two, until these new treatments are more fully evolved. These bridge one therapies and lifestyle choices will help you avoid or significantly delay irreversible physiologic changes (heart attacks, strokes, and dementia). Then you will be able to take fuller advantage of the powerful bridge two gene-based therapies. Soon after that, you'll benefit from the bridge three Nanotechnology-AI Revolution, which will mean that damage to your body that is presently irreversible will, in principle, be correctable.

1.2.4.1 Evaluating SNPs

It is estimated that each person may carry as many as one million single nucleotide polymorphisms (SNPs) [A. Braun, quoted in (Duncan 2002)]. One aspect of predictive genomics attempts to identify the most significant SNPs to determine how likely you are to be predisposed to develop a specific disease or health risk, and to evaluate the possibility that this condition might appear under particular environmental circumstances or lifestyle choices (Ames et al. 2002). Genomics testing panels are now commercially available for up to three dozen or so SNPs at a cost of less than $30 per gene, while only a few years ago, it was rare to get a genetic test done for less than $300 each. Testing is currently offered by 23andMe, Navigenics, Decode Genetics, and SeqWright. Within a few years, in accordance with Ray's Law of Accelerating Returns (Kurzweil 2005), for the same thousand dollars, you will be able to get a panel that reads your entire genome. By the end of the decade, you will probably have access to DNA chips that will test for most, if not all, of the 3.6 million SNPs currently identified. In the spring of 2007, Nobel Laureate James Watson, 79, had his entire genome sequenced by Life Sciences, Inc. of Connecticut in collaboration with the Baylor College of Medicine in Houston. The total cost of this project was more than $1 million (Davies 2007). The results of his genome were published in Nature in April of 2008 (Wheeler et al. 2008).

A SNP that can be beneficial to a person in one circumstance can be harmful under different conditions. For example, consider the "thrifty gene." This is an SNP that helps people survive on minimal calories and throughout history has given individuals a better chance of survival during periods of famine or near starvation. Today, however, this gene creates more problems than benefit, since carriers are more predisposed to obesity under conditions of excess or even merely adequate calories. Years ago, when famine was a regular occurrence, Pima Indians from the Southwestern United States, who carry copies of this gene, were better able to survive long periods of near starvation. Since this gene conferred a survival advantage, it became more prevalent in this population. But this has led to the majority of modern-day Pima Indians being overweight and having a high rate of diabetes, so it is now a disadvantage (http://diabetes.niddk.nih.gov/dm/pubs/pima/obesity/obesity.htm).

Almost all of the most common, disabling, and deadly degenerative diseases of our time, including cardiovascular disease, cancer, Type-2 Diabetes, and Alzheimer's disease, are the result of the interaction between genetic and environmental factors. Tests for some of these genes are now available. Genomics testing allows you to gain a deeper understanding of your individualized health risks and develop more specific and effective interventions.

1.2.4.2 Problems with Genomic Testing

Even if you could know all of the hundreds of thousands of SNPs you possess, like James Watson (or Craig Venter, who also had it done), the information overload would be a major problem. No one knows what to do with most of the information.

We need to wait for the bioinformatics scientists to catch up and provide us with sophisticated computer programs that can make sense of the enormous amount of data. Today's clinicians who have started to use genomics testing, therefore, limit screening to just a few of the more common polymorphisms.

In addition, not many patients would want to know that they have a genetic problem that can't be treated by any presently available therapy. For example, many women whose mothers have been diagnosed with breast cancer frequently delay testing for the BRCA1 gene, since a positive test suggests a high likelihood of developing breast or ovarian cancer themselves (Lancaster 1997). Most wait until they have had children to do the testing, since the only treatment for a positive test is prophylactic bilateral mastectomy and possible oophorectomy. As a result, most present-day testing focuses on the hundred or so SNPs that can currently be modified through interventions such as diet, lifestyle, nutritional supplements, or prescription pharmaceuticals.

1.2.4.3 The Complex Benefits of Genomic Testing: Apo E

The Apo E (Apolipoprotein E) polymorphisms are genetic markers associated with varying degrees of risk for cardiovascular disease and Alzheimer's disease and provide a good example of the benefits of genomic testing. We will first examine the specific risks and benefits associated with the different Apo E polymorphisms, and then describe how this information can prompt specific lifestyle recommendations, which can help an individual modify the real-life risks of the more dangerous genetic variants.

Apolipoprotein E comes in three alleles: E2, E3 and E4. Because of very minor differences in just one or two of their amino acids, they each differ significantly in their ability to carry fat and cholesterol in the bloodstream. Apo E2, for instance, is quite effective at clearing cholesterol from the arteries, while Apo E4 is much less efficient (Li et al. 2003).

If you possess one or two copies of the E4 allele, you may have an increased chance of having elevated cholesterol, triglycerides, and coronary heart disease (Eto et al. 1988; Singh et al. 2002). Even more important, Apo E4 is also correlated with a significantly increased risk of Alzheimer's disease (AD). If you do not have any copies of Apo E4, you have a 9 percent risk of developing AD by age 85. If you have just one copy of the gene as the E3/E4 genotype, which is carried by more than 25 percent of the population – you have a 27 percent chance of developing AD by the same age; in other words, triple the risk. But if you have two copies – the E4/E4 genotype – the risk rises to 55 percent, a sixfold increase (Kamboh 1995; Myers et al. 1996; Farrer et al. 1997). Furthermore, the average age that AD is diagnosed is much younger, depending on the number of copies of Apo E4 carried: 84 years old if you have no copies of E4, 75 years if one copy, and around 68 with two copies.

The Apo E2 gene, on the other hand, appears to confer some degree of protection against the development of Alzheimer's, and patients with at least one copy of E2 have a 40–50 percent reduction in their AD risk at least through age 80 (Kardaun

et al. 2000; Sando et al. 2008). Apo E2 is not perfect, however, because some forms of heart disease are more common in patients with this allele.

The Apo E3 form is the most common – more than 60 percent of the population is E3/E3. This allele affords some protection against both heart disease and AD.

Although the Apo E4 is a significant risk factor for Alzheimer's and may be associated with other forms of dementia, most people who carry the Apo E4 gene still do not develop dementia, and about one-half of patients diagnosed with AD do not possess any copies (Slooter et al. 1998). In some studies, the proportion of patients with dementia that is attributable to the Apo E4 allele is estimated to be about 20 percent.

But if there were no benefits associated with Apo E4, it probably would have been selected out of the gene pool long ago. People who carry this gene have a much lower incidence of some serious diseases, such as age-related macular degeneration (AMD), the leading cause of blindness in the developed world (Hamdi and Keney 2003). Meanwhile, people who carry the more favorable E2 are at much higher risk of losing their vision to AMD (Friedman et al. 2007).

Free-radical damage appears to play a key role in developing the specific type of damage seen in AD (Retz et al. 1998). Consequently, when we find that an individual possesses the Apo E4 gene, we feel special efforts to limit free-radical damage should be implemented. Apo E4 carriers should begin taking aggressive free-radical damage-control measures as early in life as possible.

Predictive genomics testing is available today that can provide previously unknowable genetic information personalized to each individual. This new medical specialty is in its infancy, and, as with any new science, there are perils and pitfalls. But today's primitive, incompletely understood tests will lead rapidly to ever more sophisticated analyses. Today's limited view of the genome will ultimately lead to significant breakthroughs in personalized medicine in the years ahead.

1.3 General Perspectives on the Bridges to Come: Accelerating Progress in Nature and in Technology

The coming of predictive genomics is just one indication that information technology is increasingly encompassing everything of value. It's not just computers and electronic gadgets. It now includes the field of biology. We're beginning to understand how life processes such as maturation, disease, and aging are manifested as information processes and gaining the tools to actually manipulate and change those processes.

The acceleration of information processes is inherent in evolution, which is essentially a process of creating more sophisticated information structures. Evolutionary processes work through indirection. Evolution creates a capability, and then it uses that capability to evolve the next stage. That's why the next stage goes more quickly, and that's why the fruits of an evolutionary process grow exponentially. Today we can see this effect in the form of a doubling of capability and

capacity of our information technologies such as computers and communication networks every year.

But we can also see this process going back to the dawn of biological evolution. The first paradigm shift in biological evolution, the evolution of cells, and in particular DNA (actually, RNA came first) – the evolution of an information processing backbone that would allow evolution to record the results of its experiments – took a billion years. Once DNA and RNA were in place, the next stage, the Cambrian explosion, when all the body plans of the animals evolved, went a hundred times faster. Then those body plans were used by evolution to concentrate on higher cognitive functions, which evolved in only millions of years. Biological evolution kept accelerating in this manner. Homo sapiens, our species, evolved in only a few hundred thousand years, the blink of an eye in biological evolutionary terms.

Then, again working through indirection, biological evolution used one of its creations, the first technology-creating species, to usher in the next stage of evolution, which was technology. The enabling factors for technology were a higher cognitive function with an opposable appendage, so we could manipulate and change the environment to reflect our models of what could be. The first stages of technology evolution – fire, the wheel, stone tools – only took a few tens of thousands of years.

Technological evolution has continued to accelerate. Half a millennium ago the printing press took a century to be adopted, half a century ago the first computers were designed pen on paper and were wired with screw drivers. Now computers are designed in only a few weeks' time by computer designers sitting at computers, using advanced computer-assisted design software. The computer in your cell phone today is a million times smaller and a million times cheaper than the computers that existed when the authors of this chapter started college 40 years ago, yet they are a thousand times more powerful. That's a billion-fold increase in price-performance in about 40 years, which we will do again over the next 25 years since the rate of exponential growth is itself growing faster.

These trends are rapidly bringing us closer to the advent of bridge two and bridge three.

1.4 Bridge Two: The Biotechnological Revolution

One of the profound implications of accelerating progress stems from the fact that we are coming to understand our biology as a set of information processes. We have on the order of 23,000 little software programs inside us called genes. These evolved in a different era. Thousands of years ago, it was not in the interest of our species to live past child-rearing, as food and other resources were very scarce, and life expectancy was in the twenties.

As an example of the outdated "software" that runs in our bodies, one of those programs, called the fat insulin receptor gene, says, basically, "hold onto every calorie because the next hunting season might not work out so well." Now that we live

in an era of abundance, that gene underlies an epidemic of obesity, and we'd like to change that program.

We now have new technologies that for the first time allow us to reprogram the outdated software that underlies our biology. Doing this is the essence of "bridge two." RNA interference, where we put fragments of RNA inside the cell as a drug, can effectively inhibit selected genes. RNA interference is capable of effectively turning genes off by blocking the messenger RNA expressing that gene (see also Chapter 21).

When the fat insulin receptor was turned off in mice at the Joslin Diabetes Center, the mice ate ravenously yet remained slim. They didn't get diabetes or heart disease and they lived 20 percent longer: they got the benefit of caloric restriction without the restriction, and there are several pharmaceutical companies that are developing fat insulin receptor (FIR) gene inhibitors for the human market. The FIR gene is just one of the genes we'd like to turn off, and there are over a thousand drugs in the development and testing pipeline using RNA interference.

We also have effective new means of adding new genes, not just to a baby but also to a mature individual. A company that the authors advise (United Therapeutics) has a process in which it takes cells out of the body (lung cells in this case), adds a gene in-vitro, inspects that the gene got added correctly, then multiplies the cell with the new gene a million fold (using another new technology) and then injects these cells back into the body. These new cells migrate back to the lungs, and this technique has cured a fatal disease (pulmonary hypertension) in animal models and is now undergoing human trials. There are hundreds of such developments now in the pipeline.

The new paradigm of rational drug design involves a deeper understanding of the information processes underlying biology, the exact sequence of steps that leads up to a process like atherosclerosis, or cancer, or insulin resistance, and then provides very precise tools to intervene. After we design these drugs using computer-assisted design tools, we can test them using biological simulators, which are also scaling up in accuracy and scope at an exponential pace.

1.5 Bridge Three: Miniaturization, Nanotechnology, and Artificial Intelligence

1.5.1 Nanotechnology

Another exponential process is miniaturization, which will lead inexorably to nanotechnology, our "third bridge" to maximum human life extension. We've begun to demonstrate the feasibility of actually constructing devices at the molecular level that can perform useful functions. One of the biggest applications of this, again, will be in biology, where we will be able to go inside the human body and extend its range beyond the current limitations of biology.