THE 55: A First Introduction

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Welcome to Michael Rose's 55, an overarching context that will enable you to use nature's rules to make sense of your health and take action to make your life much better.

You will do this by changing how you live. Not as a result of yet another fad but as the result of knowing the scientific context. You will be the agency of your own health.

Up until now, for most of us, medicine has been the controlling authority of health. And that medicine has been reductionist and simplistic. For that is how physicians have been trained to see the human body. The connections between the parts got lost in the desire to find simple-minded answers in the parts. Connections between people and their environment were obscured because of the medical-industrial focus on parts, and their mechanical explanation, modification, and treatment.

In this machine-world of crude control, the vast and subtle networks that underpin biology have been ignored and trampled. Everything was made simple for only the simple could be controlled. Everything had to be explained by simple conveyor-belt pathways, and treated accordingly. To be healthy, we were told, we had to become compliant patients, we had to give up on our true human nature.

To do well in the medical-industrial world, we had to take drugs and suffer mutilating surgeries, even for the most trivial problems. If you are diabetic, take insulin. Wrinkles and sags, get cosmetic surgery. Uncontrollable appetite, bariatric surgery. A diagnosis of heart disease is treated first with drugs, then bypass surgery, and finally a transplant.

But the new biology of our time, born circa the year 2000, is showing that this brutal style of medicine is not just inefficient. It is in fact directly contrary to the subtle networks that sustain life itself. It violates our evolutionary history, and it rapes the health that evolution gave us.

Just as Einstein and the modern physicists banished simple-minded physics, 21st Century biology is demolishing the crudely mechanistic thought of molecular biology. In its place we now see glittering webs of life. And these webs are not just mystical objects fit only for worship. Rather they are the very stuff from which the new sciences of life are being spun.

Using the 55, we will show you how you can use the new biology to take a better approach to your health, to your body, and to the way you live in the world. From this new way, you will find the comfort and the understanding that you used to give up when you entered the clinics and the hospitals that have been the temples of the reductionist thuggery of the 20th Century medical-industrial complex.

55 Theses on the Power and Efficacy Of Natural Selection for Sustaining Health

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Out of respect for both science and medicine, the following propositions are open for discussion throughout the World-Wide Web.

Preface

These theses are intended to supply a re-visioning of the scientific foundations of health and medicine. Rather than making small adjustments to a body of medical knowledge which has been developing by accretion since the time of Hippocrates, this re-visioning starts with a firm rejection of the present reductionist foundations of medicine. The human body is not an inert vessel that can be fairly viewed in terms of a definable set of chemical reactions. Rather, it is a product of an evolutionary process that has been ongoing for billions of years, an evolutionary process that has been directed by natural selection. As such, it will be argued that evolutionary biology provides the only secure foundation for understanding our health and for improving the practice of medicine.

There are two misunderstandings that this basic statement might engender, misunderstandings which must be immediately flagged as errors. I will now dispose of these errors, before getting on with the main business at hand.

The first misunderstanding would be the notion that the present perspective marks a break from scientific materialism, that somehow it is being proposed that there is something basically wrong with physics, chemistry, or even organic chemistry. Such an interpretation would be quite wrong. All of physics and chemistry are fully accepted on the present view. Instead, what is rejected is the conjecture that physics and chemistry supply enough in the way of scientific theory or experiment for understanding the foundations of health and medicine which, as argued here, are evolutionary. But evolutionary theory is built on top of the physical sciences, and does not tilt against them.

The second misunderstanding would be that the present effort is an attempt to merely add evolutionary ideas to conventional reductionist biology and medicine. Some scientists have made such attempts, and those attempts are not entirely without merit. But the present view is that the scientific foundations which are offered for medicine in the medical schools of the United States and other Western countries, with their characteristic molecular-biological reductionism, are not valid scientifically. This is not to say that such foundations were not a reasonable basis for medicine in the period from 1950 to 1975. They were. But the last 35 years of research in biology have destroyed the scientific models that held sway during those 25 years, and part of the present treatment will be to present the gist of that recent research.

THE 55: Further Introductory Notes

If you are a person who is instinctively inclined to skepticism, and is not an evolutionary biologist, let me give you an alternative way of approaching the 55 Theses.

Repeatedly in the history of our species, we have come up against key technological limits. The first proto-humans developed the core adaptation of technology some four or five million years ago. That is, they were the first species to adopt the use of hand-held tools, extensive food preparation, and the like to escape the basic animal niche based on built-in weapons and raw foods. Ever since, our evolutionary history and our biological fitness have been determined by our use of technology.

For the first few million years of our evolution, we were chiefly gatherers and scavengers, subsisting on a varied diet. We obtained access to food by using digging and cutting implements, and we fostered our digestion of that food by cleaning, pounding, cooking, and otherwise preparing it. During that time we evolved an increased capacity to digest starches, probably from the consumption of underground storage organs, like cooked tubers. We evolved adaptations for walking efficiently and handling our tools effectively.

Next our immediate ancestors spent one or two million years evolving adaptations for hunting, which was added to our already diverse repertoire of behavioral adaptations for finding food. During this period, we became markedly more intelligent than all other animals for the first time, in part because we could get the nutrients to build and sustain large brains. During this period our bodies adapted to high levels of meat and animal fat consumption.

Quite recently, evolutionarily speaking, some human populations adopted the systematic cultivation of grass species, like wheat, and the husbandry of other mammals for their milk. Such populations were then strongly selected for physiological adaptations to an evolutionarily novel diet.

This is a complicated evolutionary history, with three significant changes of direction. Taking this complex evolutionary history into account requires a deep understanding of how natural selection does, and does not, produce effective biological adaptations. Such adaptations, and their limitations, determine human health.

Unfortunately, these evolutionary foundations for human health have been generally neglected by most biologists. The medical establishment has been dominated by the reductionist cell-molecular wing of biology, which has had limited interest in evolutionary research, and even less understanding of its results. Thus extremely crude views of the evolutionary foundations of human health have prevailed in medical schools, and in the practice of medicine. On the other hand, the very few evolutionary

biologists who work in the universities of our time have paid little attention to the foundations of medicine. There are too few of us, we generally feel, so we focus on sustaining the flickering fires of our field against the prevailing intellectual darkness of present-day biology.

The consequences of this failure to engage with the evolutionary foundations of human health are all around us. Modern-day medicine is effective when it is confronting threats that are not complicated evolutionarily, such as mechanical injuries and some acute infections. But it has singularly failed to address the majority of ailments that now impinge on the world's population, from the new epidemic of type 2 diabetes to rampant cardiovascular disease and cancer. Against the chronic diseases of our time, medicine has tried remedies from the palliative to the heroic. But cure and prevention have been generally wanting.

The result is an economic and political calamity. Few of the industrialized economies have a fiscal solution for the tidal wave of aging and impaired adults that is hitting them. When a large fraction of adults cannot work because of chronic disease, their retirement from the work-force and the expense of their ineffective medical treatment are not affordable.

The only way to escape this aging tsunami is to bring about a radical solution to the medical problems of aging, where the insight that this is the key systemic problem facing most countries is spreading rapidly at this moment. The problem facing us now is how to achieve this solution.

Molecular and cell biologists propose that we increase the resources devoted to their ad hoc scrambling after a solution to the aging problem. After decades of failure to make much scientific progress, they want even more resources to continue down their path of futility, where aging is concerned.

At the same time as the reductionist biological orthodoxy has singularly failed to scientifically solve the problem of aging, evolutionary biology has made rapid, radical, and sustained progress with the same scientific puzzle. Preventing us from bringing evolutionary biology's scientific resources to bear on the practical problems of human aging, as the reductionist biomedical establishment has done, will ensure economic and political catastrophe.

In the 55 Theses themselves, I outline an alternative view of health based on evolutionary research. In the ancillary explanatory material that accompanies these theses, I attempt to provide means of unpacking and understanding the 55 for those who are not evolutionary biologists. Once the 55 have been discussed widely and openly, we can see if the current vested interests can be circumvented in order to rescue our health and our political economies.

THE 55: The Scientific Challenge

Biology is in a state of transformation. Much like the re-foundings of biology that took place after 1800, 1859, 1900 and 1952, the first decade of the 21st Century has seen a major upheaval in biology. The four previous revolutionary episodes in biology arose from the founding moments of non-creationist scientific biology, evolutionary biology, genetics, and molecular biology, respectively. The present revolutionary episode comes from the birth of genomics, the cutting edge of 21st Century biology.

The genomic revolution has shown us that genome sequences, gene regulation, and gene function are vastly more complex than previously thought. The conceit that we could unravel, dissect, and explain most biological functions in terms of simple molecular-genetic pathways is defunct. What we are facing instead is complex networks of many genes, still more transcripts, and exponentially more molecular interactions underlying each significant feature of development, function, and pathophysiology.

Traditional models for pharmaceutical development and clinical medication are now in tatters. Yet the power of the new genomic tools gives us unheralded opportunities to systematically identify the molecular and cellular foundations of infections, genetic disorders, and chronic idiopathic disorders. What to do?

It is obvious to most biologists that solving non-trivial scientific problems in biology will depend on the use of bioinformatic tools to process vast arrays of genomic, transcriptomic, metabolomic, and still other omic data. The characteristic feature of such data is its sheer magnitude. But still worse is the fact that the crude syllogistic tools of traditional biological reductionism are wholly inadequate to make sense of such data.

The time has arrived for biology to re-found itself, just as it has four times already, about once each half-century. In this re-founding, the principles of complexity and quantitative analysis have to be accepted. As in the re-founding of physics at the start of the 20th Century, after Einstein's 1905 publications, we have to give up the traditional intuitive concepts of biology, just as physics gave up the simple certitudes of Newtonian physics.

But if complexity and quantitative analysis have to be fully accepted by the biology of our time, how can we master these challenges? That is, what are the fundamental tools that we can turn to in order to make sense of the new biology?

I think that the answer is clear. Biology has to be re-founded using mathematically formal theory derived from evolutionary, genetic, and molecular first principles.

Fortunately, evolutionary geneticists have been developing such tools since the 19teens, about a century ago. The application of those tools was limited, prior to 2000, by a lack of genomic data. But now that such data are at hand, indeed gushing forth, we are entering a golden age for the application of evolutionary genetic tools to the problems of biology.

This does not mean that all the work has already been done. Twentieth-century evolutionary geneticists were working in a vacuum due to a lack of critical data. As such, like sighted people emerging from a period of prolonged darkness into daylight, they now have adjusting to do. But they have the formal theoretical methods and experimental tools to solve the key problems that challenge biology in our time.

One of the first applications of the new evolutionary genetics has been a transformation of our understanding of aging. This has been my particular focus as a scientist. It is this problem, in particular, where the application of evolutionary genetics to the challenges of the new biology is particularly straightforward. This arises for two reasons. First, aging is a problem that has utterly defeated all non-evolutionary biological research strategies. Second, aging is a problem that is readily addressed by applying evolutionary genetics in the context of the new genomic biology.

In the 55 theses, I outline a 21st Century approach to the problems of aging, both as a general scientific puzzle and as a major medical challenge in our time. The 55 are thus, in my opinion, a paradigm for the new biology being born around us.

I should be clear that I do not see the 55 specific conclusions that I adduce as final. Instead, I see them as starting points for a very different approach to the scientific problems posed by aging in general, and human aging in particular. But once the 55 are adopted as starting points, it is fairly straightforward to implement research strategies for addressing the many important questions that these starting points raise.

On the technological side, I see little promise in continuing to develop pharmaceuticals and other medical treatments for age-associated disorders based on erroneous science. Yes, sometimes useful drugs and medical procedure are found adventitiously. Likewise, bridges and cathedrals were built long before modern physics got going. But once good scientific tools were made available to engineers, architects, and chemists, their ability to build better roads, buildings, and machines exploded. That, after all, is how industrial civilization was built. Likewise, I look forward to a new medicine that is founded on the radically more powerful biology which is now at hand.

1. The biological fitness of a population is the average net reproduction of its members, which in turn is determined by their capacity to survive and reproduce; biological fitness is at the core of health.

The starting point of the present theses is to take Darwinian fitness as the key foundation for understanding health. Stripped of such a Darwinian foundation, a wide spectrum of alternative definitions of health can be offered as the central focus for medicine: biochemical efficiency, athletic performance, freedom from disease, and so on. None of these definitions have particularly well-formulated scientific foundations, and certainly none of them connect to a scientific theory with the power, range, and depth of evolutionary theory. It would be interesting to provide an historically well-developed presentation of the many alternative conceptions of health that have been promulgated and debated over the last few thousand years of Western medicine, leaving aside the more exotic traditions of traditional Eastern medicine or the shamanistic practices of pre-agricultural societies. But instead, I will just get on with the task of developing of a coherent, scientifically formulated, alternative to the various confusions that are widely on offer.

Darwinian fitness is a single numerical measure which combines all the individual probabilities of survival and reproduction of a population of individuals in the particular environment in which it finds itself. The mathematical form of this measure takes different forms with different population demographies, but it can always be defined in a scientifically cogent manner.

So why is Darwinian fitness a useful place to start developing the scientific foundations of medicine? In all the biological sciences, there are few other variables for which we have such well-developed theory. Moreover, it is Darwinian fitness that is the key to the arc of evolution. This Darwinian variety of fitness is the key determinant of natural selection, and natural selection is the steering wheel for evolution.

But natural selection is not an all-powerful determinant of evolutionary processes. Instead, it is constrained, limited, and often thwarted by other evolutionary factors. Such constraints are the main theme of the first ten theses. It is not possible to think about natural selection intelligently unless the constraints on its action are kept firmly in mind. In particular, it is not a synonym for a benign, all-powerful, cosmic force that always maximizes our Darwinian fitness.

2. Natural selection reliably produces high levels of biological fitness, and thus good health, only under the environmental conditions in which it has been acting for many generations.

A common caricature of evolution by natural selection is that it produces some type of universal progress that is sustained and predictable over millions of years. Not only is this NOT how present-day evolutionary biologists think of evolution, it isn't even how Charles Darwin himself thought of the effects of evolution by natural selection. This is, unfortunately, how many naïve and perhaps temperamentally optimistic intellectuals have thought of evolution by natural selection. Perhaps evolutionary biologists have little right to complain about this; the perversions and misappropriations of Einstein's relativistic mechanics in twentieth-century popular and intellectual culture were even more ludicrous. But this misinterpretation of evolution by natural selection has certainly impeded the use of this central biological theory by medicine, because it strips evolutionary biology of much of its salience as a foundation for medicine.

The key point is that natural selection predictably acts to increase fitness only in the environments in which it has long acted. This is why, for example, colonizing other parts of our solar system is such an inherently difficult proposition. Few, or no, species on this planet have adaptations that would enable them to thrive in the environments supplied elsewhere in our solar system. At a less extreme level, most insects have extreme difficulty surviving and reproducing during circumpolar winters, as do most plants. Environmental conditions define the context for natural selection. And such environments are defined not only by physical conditions; they also involve the biological communities of species found in particular habitats, whether those species are competitors, prey, predators, or pathogens.

This constraint on natural selection is not only a matter of habitat. It is also a matter of time. Natural selection takes many generations to produce high levels of fitness in a particular environment. Since particular environments require the evolution of corresponding particular biological functions, generally called "adaptations," in order to achieve high levels of fitness, the longstanding environmental history of any population determines which specific adaptations that population will possess.

3. Health and adaptation thus reflect the action of natural selection on a population in its previous environments, not its present environment, when these differ.

For the purpose of re-founding medicine scientifically, theses 2 and 3 direct us to pay particular attention to the sequences of environments that humans have been exposed to during our evolutionary history. It is fanciful to suppose that, because our species has been in existence for several hundred thousand years of evolution, it is fully adapted to any environmental conditions that it might encounter.

And this point is still more profoundly important when we consider the extent to which our environments have been transformed over the last century of rapid technological change. Just four or five human generations are far too few to have given us adequate adaptations to our present environment. Instead, what adaptations we have, and thus the conditions under which our fitness is likely to have been maximized, reflect the impact of natural selection on our evolution prior to the advent of our present, highly technological, industrial environment.

Thus evolution by natural selection has supplied us with adaptations only to environments in which we have lived for many centuries. But this does not then immediately imply any simple or obvious set of inferences about how medicine can best manage human health or treat our diseases. For the action of natural selection is subject to still other limitations, well beyond the vagaries of environmental history.

It is these further limitations on the action of natural selection that we turn to next.

4. Natural selection results in the evolution of good health only when there is sufficient heritable variation affecting survival and reproduction.

Natural selection accomplishes nothing without an adequate and appropriate supply of genetic variation on which to act. That is why dolphins and whales breathe air in order to get oxygen to their cells; they haven't had genetic variants that natural selection could have acted on in order to re-evolve gills.

What this means for medicine is that there are a lot of good things that natural selection might have accomplished in our evolution, but didn't. The most concrete, and indeed deadly, example of this is that humans haven't evolved the capacity to give birth through their abdominal walls. As a result, for most of the last million years, one of the most dangerous things that happened to each human was being born. That's because our birth requires that our evolutionarily enlarged neonatal cranium has to pass through the narrow bottom opening of the pelvis. It would have been brilliant if natural selection had solved this "design problem," but again, like the lack of gills in whales, it didn't have any genetic variation that it could have used to solve this design problem.

In some cases, this failure of natural selection is remarkably specific at the genetic level, yet medically devastating. The hemoglobin gene that produces sickle-cell anemia when the normal gene is absent kills thousands of people every year. But in this case natural selection actively sustains this allele in sub-Saharan African populations because genomes that have one copy of the sickle-cell gene together with a copy of the normal gene are better able to resist malaria. In an ideal world, there would be a hemoglobin gene that confers resistance to malaria without causing a deadly genetic disease. But mutation has yet to produce such a variant in sufficient numbers for natural selection to make use of it in regions where malaria is common.

Thus there is an entire spectrum of medical problems which arises from this key limitation on what natural selection can accomplish. When we can conceive of a simple morphological or biochemical solution to a medical problem, it is not a falsification of the evolutionary foundations of human health that natural selection did not produce it. Natural selection is severely limited in what it can accomplish, not least because of this problem of missing ideal genes.

5. Natural selection produces good health only when population size is large enough to overcome genetic drift; inbreeding reliably impairs health in outbreeding species.

Many members of the human species have a great propensity to mate with other humans. You may know such a person yourself. This makes eminent evolutionary sense: we can't reproduce asexually or by self-fertilization. It is this absolute requirement that we had to have sex to that generated our high levels of genetic variability. We are one of nature's outbreeding species, a species in which mating is not normally kept within close families, unlike some social insects and fig wasps, or even the naked mole rats of Africa.

This feature of our mating history gives rise to a medical problem which should be more widely appreciated: mating within small ethnic groups gives rise to an increased frequency of genetic diseases caused by recessive deleterious genes. One of the most horrifying examples of this problem is the prevalence of Tay-Sachs disease in the offspring of matings among Ashkenazi Jews. Tay-Sachs is an incurable and fatal disease that causes severe brain degeneration in young children, with accompanying blindness, mental disability, and severe pain. This medical tragedy arises insidiously from the common human inclination to mate with someone from a similar background.

Generally, mating among biological relatives is associated with a wide variety of impairments, from shorter stature to lower IQ. This is an effect that natural selection abhors; as a result the best single example of an apparently inherent human behavioral pattern is an aversion to mating with siblings or parents.

This is the first thesis which leads to a simple piece of medical advice. People should either avoid having children with individuals with whom they share ancestry or, if they decide to go ahead with such a plan, they should actively seek genetic counseling and the best prenatal genetic diagnostics available. Fortunately, we are entering an era of rapid progress in genetic characterization, and we can all hope that ways will be found to circumvent the tragedies that genetic diseases produce.

6. Natural selection produces good health only when new deleterious mutations are rare or small in magnitude; very few novel mutations will have large and generally beneficial effects, in an environment to which a population is well-adapted.

Mutation is the source of the genetic variation that natural selection acts on. But very few new mutations are beneficial. Instead, the vast majority of mutations have no selectable benefit, or are actually deleterious. It is only in comic books or bad science fiction that mutations suddenly produce a much-improved human.

This has significant implications for human health. Circumstances that elevate mutation rates will generally impair health. The best example of a situation where this arises is exposure to radiation. At extreme levels, radiation directly degrades biological tissues, causing immediate death in the worst cases.

But more subtly, radiation also readily increases mutations rates in exposed tissues. In somatic tissues, such mutation can lead to combinations of mutations which allow unlimited cell proliferation. When somatic selection among such mutant cells operates over time, selection within the body can favor the most proliferative of these mutant somatic cells, leading to the development of malignant cancer.

In the cells that will eventually produce sperm or eggs, mutation will lead to mutant genes that can be transmitted from generation to generation, potentially causing a trail of havoc in the descendants of the individuals whose testes or ovaries were irradiated.

The obvious medical significance of these basic points it that we should avoid exposure to radiation. There are five contexts in which we are routinely exposed to elevated levels of radiation: (i) sun exposure; (ii) diagnostic medical or dental radiology, (iii) high-elevation flight, (iv) radon emissions from basements, and (v) proximity to radioactive wastes, such as those produced by nuclear power plants, mining, and medical radiology. This is a spectrum of exposure risks from the unavoidable to the relatively rare and avoidable.

In addition to radiation, there are a number of synthetic and naturally-occurring substances that cause mutations as a result of chemistry alone. Most of the worst of these are products of scientific or industrial chemical synthesis. On the other hand, Bruce Ames and others have found weaker carcinogens in many of the food products that we routinely ingest, from caffeine to burnt meat.

7. Natural selection will sustain nucleotide sequences that foster biological fitness however numerous and however indirect their benefits, making the genetic foundations for the evolution of health genome-wide and complex.

The kinds of experiments that most biologists favor involve studying large-effect mutations and other ways of mutilating or disrupting experimental animals. It is an irony of much molecular genetic research that it often studies the physiology of large-effect mutations produced by radiation and other means. Experimental animals with such mutations are unlikely to be a useful guide to the physiological variation that arises from the kind of high-fitness genes that are more likely to be common in large human populations. Yet molecular biologists are fond of reasoning from (a) the large experimental signals that such mutants produce to (b) the functional underpinnings of normal physiological function.

Sometimes this works. If a biologist carefully destroys the reproductive organs of a group of animals using irradiation or genetic engineering, but does not inflict severe adverse side-effects, these animals will usually live longer compared to intact controls. This reveals a cost of reproduction that is one of the more durable, if not quite universal, findings of research on aging. An interesting exception is women, who do not appear to live longer if they undergo hysterectomy and ovariectomy. But men, at least in American institutions that used to castrate incarcerated "mental defectives," who are castrated do live longer.

On the other hand, producing inbred laboratory stocks and then mutating them has been shown to give misleading results in a significant number of cases. This doesn't mean that such experiments can never be used to reveal how animals work. But it does mean that such experiments can't be generally trusted.

As an alternative approach, evolutionary biologists, quantitative geneticists, and other types of more Darwinian biologists prefer to work with naturally occurring genetic and environmental variation. This reflects the common assumption among such biologists that natural selection will often favor genetic variants and physiological responses to environmental variation that are limited in their effects, rather than large in their effects. Furthermore, this kind of biologist generally supposes that genetic variation at many sites throughout the genome will underlie the evolution of functional characters, like those which sustain both Darwinian fitness and medical health.

One way of looking at this difference between these two types of biologists is that the first type, let us call them molecular biologists or reductionists, like to suppose that organisms are assembled from well-defined, machine-like, large-effect pathways. The second type of biologist allows that a few cases like that may evolve, but that much of the underpinnings of normal function is genetically and physiological complex. Let us

call these Darwinian or evolutionary biologists, as this is fairly close to Darwin's own thinking on this topic. Darwin and subsequent generations of evolutionary biologists have emphasized that natural selection can act on many inherited variations, even relatively subtle heritable genetic differences. Thus a Darwinian view of health is naturally inclined to emphasize the idea of many contributing genetic and biochemical factors underlying healthy function, not a small number.

8. This complex genomic foundation for adaptation in turn produces a still more complex network of interacting molecules that sustain survival, health, fertility, and function.

Arising from the genetic complexity of healthy function is a still more complex set of interacting products of DNA sequences: all the RNAs transcribed from DNA and all the proteins that are made from RNAs. These in turn interact with each other, with other molecules that make up cells, and even with the DNA from whence they came.

So the genomic complexity of the DNA that underlies health is just the simplest dimension of healthy function. What is erected from the linear strands of DNA that make up our genomes is three-dimensional, and teeming with a fury of interactions. Many of these interactions happen quickly, while others proceed only slowly. But this network is all in motion and in interaction.

It has been the long-standing, indeed hubristic, conceit of molecular and reductionist biology that this vast three-dimensional matrix of furiously interacting gene-products can be understood using such simple linear paradigms as their concept of pathways.

It is indeed correct that there are some major channels that weave their way through the hurly-burly within cells, and among cells within organisms. But focusing solely on these major channels of biological causation would be like an attempt to understand the population and economy of Los Angeles in terms of its interstate freeways alone. Yes, cutting these freeways, or diverting them wholesale, has a major impact on the economy of the Southern California conurbation. But determining the impact of such wholesale disruptions is very different from a satisfactory analysis of the complexity of this urban region's economy.

Thus, in developing a useful understanding of this complex three-dimensional web of cellular and organismal function, we need to use conceptual tools that are adequate to the task. Unfortunately, the reductionist toolkit of traditional 20th Century molecular and cell biology simply is not adequate, in strictly scientific terms. It isn't just crude and mechanical. It is wrong.

Instead, we must look to such open-ended intellectual tools as population genetics, quantitative genetics, and systems biology to make sense of the explosive complexity of biological function. And such tools are inherently mathematical and computational.

9. The forces of natural selection weaken with adult age in species that have distinguishable adults and no fissile reproduction.

We now face the prospect of developing a 21st Century biology based on formal, mathematical, and computational tools. It is from this 21st Century biology that a new medicine for addressing our chronic health ailments will arise, those health ailments that are lumped together in medicine's wastebasket called aging.

So, which formal, mathematical, and computational tools should we start with?

Many of the key applications of 20th Century physics grow out of its key equations. Atomic power and atomic bombs both grew out of Einstein's result that $E = mc^2$. Television arises from the mathematics of the photoelectric effect, the result for which Einstein received the Nobel Prize. And so on.

Are there mathematical results of comparable significance for 21st Century biology and medicine?

Yes, there are. The first 8 of the 55 theses derive both directly and indirectly from basic quantitative results from evolutionary genetics. With this thesis 9, however, we come to the most important equations of all for the new medicine of chronic disease, those of Hamilton's (1966) Forces of Natural Selection. In the references supplied with the 55, you can see the algebraic forms of the equations for these Forces, as well as graphical plots of them. But in these 55 theses, I will explain them in verbal terms for the mathphobic who have had their quantitative imaginations neglected or destroyed by their formal education.

Hamilton derived two Forces of Natural Selection in 1966. The first scales the impact of natural selection on the rate of mortality at each and every age, from birth to infinitely great ages. [Mortality refers to the probability of dying at a particular age.] The second scales the impact of natural selection on fecundity at each and every age, from birth to infinitely great ages. [Fecundity refers to the quantitative output of offspring at a particular age.] These two forces are among the most important formal results ever obtained by scientists.

10. When the forces of natural selection weaken with adult age, declining survival and fertility evolve in adulthood, and thus produce the decline in health which is commonly called 'aging.'

In animals like mammals and insects, the Force of Natural Selection acting on mortality proportionately scales as follows. Childhood: From birth to the start of reproduction in a population, it acts with 100% of its maximum force. During this phase of life, therefore, natural selection acts strongly to sustain our inborn health, in terms of our capacity to survive, which can be thought of as our basic functional integrity. Even at full strength, natural selection won't always succeed; accident, contagious disease, and mutation can all degrade health during the childhood years. But it does a damn good job. Aging Phase: From the earliest ages of reproduction until the last age of reproduction, the mortality force steadily declines. During this phase of life, natural selection progressively weakens its evolutionary surveillance of our health, resulting in predictable, general, and sustained declines in our health. Late-life Phase: After the last age of reproduction, and forever after, age-specific natural selection is gone. At this point, our health is sustained only by the age-independent health benefits built by natural selection for earlier ages. However, in many animal populations, this late-life phase features relatively reasonable health, and the preservation of some useful function, under protected conditions. But it does not among humans in industrial countries, an issue that we will discuss in detail later in the 55.

In animals like mammals and insects, the Force of Natural Selection acting on fecundity scales as follows. Childhood: From birth to the start of reproduction in a population, the fecundity force usually progressively falls. However, since we do not reproduce during this period, this has no observable effect. Aging Phase: During the earliest ages of reproduction, there is usually a transitional period during which fecundity increases rapidly with adult age. This can be thought of as the developmental result of all the quantitative effort that natural selection is putting into enabling the adult organism to develop the anatomical structures, physiological functions, and reproductive behaviors required for successful reproduction. Thus, in teen-aged humans, the first years of basic reproductive capacity are marked by relatively poor fertility, inappropriate or misdirected sexual behavior, and poor parenting behavior. But quickly, the adult human develops its full reproductive capacity, at around the age of 20 years in men, somewhat later in women. After that, fertility falls with age, the other side of declining health during adult life. Note that in mammalian species, which have a great deal of parental care of offspring, an infertile adult caring for their immediate offspring is still effectively reproducing. That is to say, in evolutionary terms female reproductive function extends past menopause. Late-life Phase: After the last age of survival in the evolutionary history of a population, age-specific natural selection for the maintenance of fecundity is gone. During this epoch of life, our reproductive functions are sustained only by age-independent benefits built by natural selection for earlier ages.

However, in many animal populations, this late-life phase features measureable reproductive function. But it does not among humans in industrial countries, an issue that we will discuss in detail later in the 55.

11. If the forces of natural selection are strengthened during later adulthood, improved later health will evolve if natural selection is not impeded by very small population sizes, environmental change, or an absence of heritable variation.

There are a variety of ways to show that the Forces of Natural Selection provide the key factor in determining the evolution of the pattern of functional decline called aging. Some of them will be discussed in subsequent theses of the 55. But there is a strikingly simple pattern of comparative variation among different species of animal which makes the point fairly well, and you don't need much biological background to understand it.

Consider turtles. Turtles come in very different shapes and sizes, some of which live out almost all their lives in oceans, like green sea turtles. Other types of turtle live in marshy wetlands. And we can consider tortoises, like the giant Galapagos Tortoises, as part of the overall turtle group, too. They almost never go swimming.

Some turtles and tortoises have very thick shells. Furthermore, many of them can retract their head and limbs inside these shells when they are attacked. Some of them, furthermore, have powerful biting mouths, which you would be ill-advised to place your fingers inside. When turtles and tortoises with these thick shells are maintained in zoos, they can live for very long periods of time, during which some of them maintain active sex lives. I have seen Galapagos tortoises at the San Diego zoo which are much older than I am, some probably at least 90 years of age. They still live with only modest medical care provided by their veterinarians.

On the other hand, soft-shelled turtles have much shorter lifespans, often less than twenty years, even when they are compared with hard-shelled turtles and tortoises of similar size. Why should this be so?

It is a basic feature of the Force of Natural Selection acting on mortality that a population which has suffered higher rates of mortality in its evolutionary history will tend to have its force decline faster with adult age, when everything else is equal. Soft-shelled turtles are not as good at defending themselves against predators as turtles with harder shells. Therefore, evolutionary theory predicts that they will evolve shorter lifespans, because of a faster decline in their forces of natural selection acting on mortality.

This concept readily generalizes to the following contrasts: similar species with and without venom, the venom giving better defense against potential predators, and the evolution of longer lifespans; similar species with and without flight, flight allowing ready escape from predators, and the evolution of longer lifespans; in general, larger animals are harder for predators to subdue and eat, so those species too tend to live

longer. Sometimes multiple factors differ between species, such as larger snakes with no venom (like boid snakes) which may or may not live longer than smaller species with venom (like cobras). But when other factors are similar, an attribute that strongly reduces mortality levels will usually lead to the evolution of longer lifespans, when similar species are compared under good laboratory or zoo conditions.

12. Aging is a pattern of declining or de-tuned adaptation that is correlated with adult age only because adult age is at first strongly correlated with declining forces of natural selection.

We have all seen sunrise and sunset. In everyday language, we are describing a subjective experience of relative motion. But the sun doesn't actually revolve around the Earth. It is just an optical illusion produced by the spinning Earth.

We have all seen the physiological deterioration of aging, or experienced it ourselves, which seems like a physiological process, akin perhaps to the filtering of our blood by our kidneys leading to their production of urine. Thus molecular and cellular biologists characterize aging in terms of hypothesized chronic physiological processes which are parallel to the production of urine. One of the most popularly hypothesized aging processes among such molecular biologists is free-radical damage, which non-biologists can think of as similar to rusting metal: progressive, cumulative, chemical damage involving oxidation.

In terms of the view articulated here, in the 55, this is as legitimate an inference as assuming that the sun revolves around the Earth. Aging seems exactly like cumulative damage, just like it seems to the uninformed that the sun revolves bout the Earth. Let me be clear. The Moon does orbit the Earth, as do many man-made satellites. You can suffer cumulative damage: your knee's connective tissue will be progressively damaged if you repeatedly run marathons on pavement. So Earth-centered orbiting and cumulative damage are both processes that occur. The key scientific questions, though, are whether every celestial body orbits the Earth, and whether all the physiological impairments that accumulate during adulthood are due to cumulative damage. Most people know that the first hypothesis is false. Here the view is that the second hypothesis is also false.

We know why it seems as if the sun revolves about the Earth. It's due to relative motion.

And some evolutionary biologists know why it seems as if aging is a process of cumulative chemical breakdown with adult age: Hamilton's Forces of Natural Selection fall VERY predictably with adult age, ensuring that most animals will show palpable processes of deterioration. [The ones that don't age effectively lack this fall in Hamilton's Forces, for reasons we will discuss later.]

These conclusions don't mean that there are no celestial orbits, or that there is no physiology involved in aging. A heliocentric solar system still has orbits, and the evolution of the aging still involves physiology. But aging is not a merely physiological, biochemically driven, process of cumulative damage. It is, instead, something else altogether. And the difference between these two views of aging is full

of radical scientific consequences. And yet further, the difference between these two views of aging is fraught with still more radical medical implications.

13. The declining forces of natural selection lead to an evolutionary failure to establish the genomic information required for tuning the complex networks of life well enough to provide a high level of health indefinitely; there is no mechanistic necessity at the level of physiology to this failure.

It is intuitively hard for people who have never seen diagrams of solar systems to absorb the concept of a heliocentric solar system, in which the Moon orbits Earth, but Earth orbits the sun. But with such diagrams and a patient science teacher, most people get over the naturally-geocentric intuitive view.

It is still harder to get people to absorb the present-day Darwinian explanation of aging, as derived from Hamilton's Forces of Natural Selection. I have been failing at this task for decades, and I am not alone. The problem is that the meaning of the equations and scientific diagrams that we use to explain the theory is not as intuitively accessible as diagrams of solar systems.

But I recently thought of another way to convey the idea. The key is to understand that animals and the cells that they are made from are extremely complex machines that function because of information stored in their genomes. That information is built by natural selection. When natural selection is impaired, by mutation or inbreeding for example, the information underlying function is degraded. That is, functional information from the genome is built by natural selection, to the extent to which natural selection can, given the evolutionary situation.

Some of this information is age-specific. So there is genetically encoded information that effectively "instructs" the mammalian fetus how to develop prior to birth. There is also genetically encoded information that effectively instructs the developing mammal to undergo a process of sexual maturation, in order to reproduce. All this information was produced in our evolutionary past thanks to the full force of natural selection acting at ages before the start of reproduction.

But natural selection has been under little pressure to specify instructions for useful function at later adult ages. It is not that there are material difficulties with sustaining life which natural selection cannot overcome; as we will discuss later in the 55, natural selection can easily do so. It is just that natural selection hasn't bothered to develop the information for our indefinite survival. The information isn't there. There is nothing to "read off" of the genome with which to sustain our youthful health. Those pages of our genomic instruction manual are either blank or defaced.

Unlike God in Woody Allen's movie "Love and Death," natural selection is not an underachiever when it comes to our aging. It just doesn't care. Or you can think of it as a novelist or screenwriter who loses interest as they proceed through the drafting of their work. The last chapters just haven't been written.

Physiologically, to the extent to which the genome doesn't have useful instructions for later survival or fertility, it is going to become harder for the animals with that genome to survive or reproduce.

14. Aging hypotheses based solely on supposed universal imperfections of molecular, cell, or organismal physiology are wholly falsified by the existence of biological species that do not exhibit falling average rates of survival and reproduction among large cohorts maintained under good conditions, a pattern exhibited by some fissile coelenterates, for example.

But there is no need for a Darwinian biologist to be particularly eloquent about the falsity of conventional gerontological theories. The images of the round Earth supplied by the NASA Apollo missions that reached the Moon obviously annihilate Flat Earth theory. Likewise, evolution has supplied devastating refutations of the cumulative damage theories of mainstream aging research.

Those refutations are the animal species that don't show aging. At all. It is now a well-demonstrated fact of aging research that there are some animals which do not show a detectable increase in rates of dying with time, even after decades of maintenance. Under the best conditions, when extremes of temperature and predation are entirely prevented, along with provision of good nutrition, some of these animal species which reproduce by splitting into similar offspring can apparently be kept alive indefinitely. For example, sea anemones are species that grow as circular tubes with fringe tentacles. Some of these species reproduce by longitudinally splitting their fully grown tubes to make two smaller tubes growing side-by-side. Then the smaller tubes grow as large as their mother, and split again themselves. Animals like these have been kept alive in aquaria, without a single one dying, over many decades. Sea anemones are species of the coelenterate group. Coelenterates that reproduce in this fissile manner only do not usually show aging. Other coelenterates that do not have any type of fissile reproduction do undergo aging.

This contrast is shown by other animal groups, such as some aquatic worms. Plants with extensive fissile reproduction, like trembling aspen trees, also do not show aging. There is nothing whatsoever in the basic cellular or organismal biology of animals and plants that requires aging. Evolution by natural selection can entirely eliminate aging, regardless of each and every feature of cumulative biochemical or other damage that whole organisms and their cells might be subject to.

Exactly why and how evolution is able to accomplish this feat is a matter we will take up later in the 55. But for now, I suggest that you contemplate a somewhat similar

feat. Each and every one of us is a collection of somatic cells that have branched off from a lineage of germ-line, or reproductive, cells that has been maintained for hundreds of millions of years, since the origins of the first vertebrates about 500 million years ago. Evolution has apparently had little difficulty accomplishing this feat for vertebrates, crustaceans, and mollusks, all of which we find ancestors for among fossils dating back more than 500 million years before the present time.

That is, there is nothing about the indefinite maintenance of lineages of cells that evolution has any difficulty accomplishing. Rather, things become different when well-defined somatic cells are produced, cells that will not become part of offspring. The reasons for this lie in the circumstances under which the forces of natural selection do not decline, as will be explained further here in the 55.

15. Aging evolves because of the previously adduced evolutionary genetic limitations to the forces of natural selection, which are affected by physiology, but aging is nonetheless not a merely physiological process.

Do the last five theses imply that physiology does not matter? No, not at all. Physiological features of organisms matter a great deal for the evolution of their aging.

Both insects and mammals are thought to age universally. That is to say, no one has ever found an insect or mammalian species in which some part of adulthood is not marked by endogenous deterioration, regardless of how diligently they are cared for by their owners, zookeepers, or attentive laboratory scientists. When studied with enough care, all these species show some type of aging pattern that features both functional impairment and increased risk of death, along with declining reproduction in those species that reproduce more than once.

But is their physiology irrelevant? Insects and mammals differ significantly in their capacity to produce new cells as adults. Mammals have a great deal of cell proliferation as adults. Insects have fairly little, with most of this cell proliferation confined to their reproductive organs and their kidney-like organs, the Malpighian tubules. Mammalian aging often features an increased risk of cancer, a disorder of highly proliferative somatic cells. Insect aging rarely features cancer; insect cell proliferation is so stringently controlled in adults that very few aging insects have been found in which cancer is detectable. It happens, but without deliberately introducing mutations in a laboratory strain, insect cancer is very rare. Thus the cell biology of mammals and insects has material effects on their patterns of aging, including the presence or absence of cancer.

This example illustrates the point that the physiological features of a group of animal species affects how their aging evolves qualitatively. Previously, we have shown how other features of a group of species affects how their aging evolves quantitatively. Thus growing a shell, or not, strongly affects the evolution of aging. Some of the longest-lived animals are burrowing bivalves, which benefit from the protection of both their burrows and their shells.

One way to think of this relationship between aging and physiology would be as follows. Physiology at every level, from molecular biology to functional ecology, conditions the mortality risks and the patterns of reproduction of a species. These mortality risks and reproductive patterns determine the terms in the equations which define the Forces of Natural Selection. Those forces then condition the evolution of patterns of aging, subject to the availability of genetic variation, rates of mutation, and other evolutionary genetic factors. So physiology certainly conditions how evolution shapes aging. But it does not require, or by itself generate, aging.

16. Among the most important physiological constraints on the action of natural selection are trade-offs between the biological functions underlying age-specific rates of survival and reproduction.

One of the most important features of physiology that affects the evolution of aging is trade-offs between functions at early versus later ages. George C. Williams felt that this was the central requirement for the evolution of aging, as he argued in his famous 1957 paper on the topic. His conclusion was that, given his then-crude understanding of the declining Forces of Natural Selection, evolution would give up later deterioration for early vigor whenever it was given the chance.

There is a great deal of theoretical, comparative biological, and experimental evidence in favor of this hypothesis. Some of that evidence will be discussed in subsequent theses. But in this thesis the chief focus will be to develop the basic idea, particularly why so many biologists think that it is important.

The idea of evolutionary and functional trade-offs is one of the ubiquitous themes of biology. And it makes perfect sense in terms of physics and chemistry. Even in terms of engineering.

Think about automobiles. It would be very hard to build a car that can carry many passengers, get great gas mileage, and have outstanding acceleration or handling, all at the same time. There are material trade-offs that impinge on the automotive engineering of such a vehicle, where many of these constraints arise from basic features of physics, such as momentum and other corollaries of the laws of motion, as well as chemistry, such as the efficiency with which chemical combustion of gasoline can generate force.

In the same way, there are material constraints that affect how quickly a large animal can develop: how big it is at birth, how quickly it can be fed, how efficiently its food can be converted into growing tissue, and so on. Biology is full of constraints, some of which arise from basic features of physics and chemistry, some of which are more specifically biological, such as rates of cell division and the time required for cells to undergo differentiation.

Thus the basic concept of trade-offs can be naturally extended to relationships among such biological processes as survival and reproduction. An insect that provisions its eggs with fats from its abdominal fat body, and then lays those eggs and flies away, won't have those fats with which to survive a subsequent period of starvation. It has used them up. It can get more nutrients, if it has mouthparts – which mayflies and some moths do not. But there is a material trade-off between resources sequestered for reproduction at early ages and resources conserved for survival to later ages. From

this trade-off, as well as many other kinds of trade-off, the idea of a material antagonism between early reproduction and later survival is entirely natural.

17. When such trade-offs arise from antagonistic pleiotropic effects of genetic variants, they sometimes maintain genetic variation for functional characters, and thus selectable genetic variation for patterns of aging.

There are two kinds of trade-off which are important to distinguish when thinking about the evolution of aging: genetic trade-offs and non-genetic trade-offs.

Cases with genetic trade-offs are called antagonistic pleiotropy, a term I invented in the early 1980s. In genetics, the term pleiotropy refers to genetic variants which have multiple effects. With antagonistic pleiotropy, genes have variants with opposed effects on different components of fitness. Imagine, for example, an allele that gives rise to faster egg-laying in young adult insects, with the antagonistic pleiotropic effect of a reduced rate of adult survival thereafter. If the increase in early fecundity is large enough relative to the reduction in adult survival, natural selection will favor the genetic variants that sacrifice later survival for earlier reproduction.

This is where the Forces of Natural Selection have a critical role to play. The key factor is adult age. If the beneficial effect on reproduction is early in adulthood, but the adverse effect on survival is late in adulthood, the biased weightings of the Forces of Natural Selection in favor of early versus late ages strongly favor the evolution of increased early reproduction and decreased later survival. In this respect, natural selection plays the role of an unfair merchant, who tips the scale in favor of themselves when you aren't looking. [That is why a Western symbol of Justice is a blind-folded woman holding up a pair of scales.] Natural selection is inherently biased in favor of early reproduction, all other things being equal.

There are three main possibilities for the evolution of genes that have antagonistic pleiotropy affecting aging. The first possibility is that survival costs of increased early reproduction are too great and too early relative to the benefits, and such genes will not spread by natural selection. The second possibility if that a gene gives rise to a significant net increase in fitness in every genotype in which it occurs. In such cases, natural selection will sweep genes like this to fixation if they arise with some frequency in a population.

The third possibility is that genes with antagonistic pleiotropy give some genotypes with increased fitness, but other genotypes with decreased fitness. In this case, such genetic variants first increase in frequency thanks to natural selection. But they do not sweep through populations all the way to fixation. They remain polymorphic, and can be detected in evolutionary and genetic experiments, revealing the antagonistic pleiotropic effect.

18. When such trade-offs can be physiologically tuned within the lives of individual organisms, natural selection may act to produce physiological machinery that provides plasticity which enhances average fitness.

One of the basic features of natural selection is its propensity to favor the exploitation of environmental contingencies. Thus, in the case of the lactose operon (an operon is a suite of bacterial genes located end-to-end) the genes for the digestion of lactose are "turned on" in the presence of lactose. Absent lactose, the enzymes that these genes produce are not produced in substantial quantities. But expose the bacteria to lactose, and its lactose operon responds by producing more transcripts of the genes for making the lactase enzyme. This is called phenotypic plasticity, where the term "phenotypic" indicates that it is not based on genetic change, and the term "plasticity" refers to change, not the involvement of carbon-based polymers that could be used to wrap food.

In cases of phenotypic plasticity like that of the lactose operon, evolution by natural selection is economizing on resources, where these resources may be material. Thus the resources involved in producing lactose-digesting enzymes include the nucleotides required to assemble the messenger RNA that carries the enzyme-building instructions from the genome. Then there are the amino acids required to assemble enzymatic protein, following the RNA-encoded instructions. There are the additional resources required to execute the protein synthesis process, such as the processing of the mRNA, the diversion of ribosomes to the task of assembling the required enzymes. Finally, there is just the metabolic time consumed with the task.

The term phenotypic plasticity is sometimes divided into two further subcategories: adaptive and non-adaptive. In the non-adaptive cases, there are no specific regulatory signals that modulate the phenotypic interactions between characters. Thus, for example, there is no specific regulatory signaling involved in the human body's response to having a hand or a foot cut off. But there is definitely an extensive plastic response, as many other aspects of the phenotype respond to such dismemberment. With adaptive cases of phenotypic plasticity, there are hormones and other signaling agents involved in effecting a phenotypic change in response, where these signaling systems generally act to increase the average fitness of members of the population when it is kept in its ancestral conditions.

Note, however, that away from the environment in which those signals were established by natural selection, the effects of such signaling may be counter-productive. A favorite example of this for many of us who are interested in the human diet is our exaggerated and probably inappropriate appetite for sweetened foods, from ice cream to sodas. Basically, in our ancestral environments, we retained the general primate taste for sweet foods, perhaps because fruit consumption is such a widespread part of the primate diet. [Note that adult cats have no such "sweet tooth." It is not

inherent among all mammals.] But in our present industrial environment, in which food companies have an incentive to exploit every addictive or otherwise exaggerated preference for particular tastes, consuming “all the sweet stuff” leads many to lives of obesity, type II diabetes, and cardiovascular disease.

19. Such adaptive life-history plasticity will sometimes produce detectable trade-offs between survival and reproduction in the range of environmental conditions that prevailed when natural selection established such life-history plasticity.

It is a general, though not universal, rule that, if you give adult animals abundant nutrition, their fertility will increase. This is true in female insects and in female rodents. Among severely undernourished women, ovulation stops. Male mammals with inadequate nutrition have reduced fertility.

The interesting thing about such situations is that, in some species, this reduced reproduction is associated with increased capacities to survive, both under acute stress and over prolonged periods. This pattern has two interpretations: (i) the inevitable side-effect of reduced costs of reproduction; and (ii) an evolved life-history plasticity which enhances average fitness. Note, however, that these two explanations are not entirely opposed to each other. In some cases, animals may face unavoidable reductions in reproduction that then benefit survival, and yet they may evolve physiological mechanisms that strengthen this enhancement of survival under conditions of moderate deprivation.

But as with other instances of adaptive plasticity, adaptive life-history plasticity will be based on contingencies and constraints that were built in ancestral environment, not necessarily current ones. Thus the patterns of phenotypic plasticity that are found among laboratory animals living in environments that are evolutionarily novel to them will not necessarily reveal their benefits.

In exactly the same way, most humans now live in industrial environments that are evolutionarily novel to an extreme degree, particularly from the standpoints of nutrition and activity. Like most, but not all, animals, we are generally selected to economize on effort. Lions will sleep for many hours in a day, hunting only intermittently. On the other hand, many herbivores graze almost relentlessly during daylight. Apparently, bonobos in the wild also seek out food rather relentlessly. As omnivores, our behavioral inclinations toward activity are probably intermediate. But I wonder about the extent to which the slothful inactivity of the middle-aged on agricultural diets arises from inappropriate signaling. The middle-aged in hunter-gatherer tribes do not seem to be comparably lethargic.

20. A single pharmaceutical or nutritional substance will never cure aging, for aging is not a simple physiological disease or dysfunction, but the de-tuning of adaptation with adult age.

The quest for a substance that might arrest aging, or even reverse it, has been perennial. We have myths and records of this quest from both Eastern and Western Eurasian civilizations. Fountains of youth, philosopher's stones, magic fruit or herbs that sustain youth, fortunate climes in which healthy centenarians live, they are all to be found in the written records of the great civilizations.

And these hopes and fables are still with us. The biotech company Geron was founded on the reductionist premise that determining how to give our somatic cells the capacity to remain "young" and proliferative would "cure the disease of aging." Their focus was on the telomeres that are the caps to our chromosomes. As human cells divide under glass in laboratories where they can be kept alive outside of our bodies, their telomeres progressively shorten. When this shortening has largely eroded the telomeric caps, cell division slows and comes to a stop. Using this idea to "cure aging" is a bit more complex than a fountain of youth or the philosopher's stone, but similar in its mythic aspirations.

Amazingly, in the 1990s, it proved possible to engineer human cells that produced enough telomerase to refurbish telomeres. The result, as the founders of Geron had hoped, was that these cells could proliferate indefinitely in human cells cultured under glass, with none of the slowing proliferation that was interpreted as "cell aging" for the last third of the 20th Century.

Geron's attention then turned to identifying substances that might keep telomerase activated in the somatic cells of our bodies. And such substances have been found. For example, a component of the Chinese herb astragalus called "TA-65" is known to foster telomerase activity. TA-65 is now being marketed as a telomerase activator by a company called TA Sciences for use as a nutritional supplement to stave off aging, rather than a drug for a specific medical condition. There have been some promising clinical results from a double-blind placebo-controlled study of the effects of TA-65. Oprah Winfrey has been quoted as saying, "I want longer telomeres." So is this the long-sought fountain of youth?

Telomerase activation exemplifies many of the difficulties with "solving the problem of aging" using the tools of molecular and cell biology. Malignant tumors have higher levels of telomerase activation, in most cases, than our normal somatic cells. This makes sense, in that cancer cells have relatively unbridled proliferation. Thus the problem for telomerase activation is that it is not necessarily good to have cells in our bodies with uncontrolled proliferation. Rather, the human body has multiple

mechanisms, including telomere shortening, which actively forestall such cell proliferation.

More cell proliferation in our bodies is a double-edged sword. It would provide more cells with which to repair tissue damage, but it might put more of our cells on the road to becoming malignant. Finely tuned to target just those cells which would be most beneficial to keep proliferating, telomerase activation might be a useful therapy. But it is unlikely to alleviate all the things that go wrong in our bodies. And turning on cell proliferation generally might actually shorten life, by fostering cancer.

21. Multiple pharmaceutical substances or nutritional supplements will only ameliorate aging to the extent that they achieve genome-wide tuning similar to that which natural selection achieves when its forces are strengthened at later ages.

So how best to use the range of candidate anti-aging substances? It is not my view that such substances should never be used. There is nothing magical, on my view, about aging. It is a result of evolution by natural selection failing to provide the physiological machinery that could indefinitely sustain the lives, and thus health, of organisms. When evolution builds organisms that can live indefinitely, it does so using perfectly ordinary biochemical machinery. In principle, there is no reason why biological science cannot emulate this feat, supplying similar machinery to keep humans alive indefinitely.

The challenge is that when natural selection builds the adaptations that sustain health, it uses quite complex biochemical machinery. This biochemical machinery is certainly not intelligently designed, because evolution always builds adaptations based on preexisting features of organisms. Evolution can't start with a blank sheet, and make elegant design decisions. The more you learn about how organisms function, from the visible machinery of organs and tissues down to the processing of individual molecules, the more you will see what a patched-together contraption your body is.

But that patching-together, that progressive tinkering, proceeds by fine-tuning hundreds of biochemical pathways in concert, not one or two. Thus the problem of intervening in the tuning of adaptation with adult age necessarily involves emulating what natural selection can accomplish. Such "anti-aging" intervention might not have to be quite as complicated as what evolution does, but it would have to be comparable in appropriateness and utility.

Thus radical anti-aging intervention requires acquiring a great deal of information about how our genomes tune our health as a first step. Then the goal would be to change that tuning so that health can be sustained. While this might seem to be a virtually impossible task, there are research strategies that can disclose how this should be done, research strategies that we will be reviewing later in the 55.

For now, it is important to keep firmly in mind that, whatever our hopes or fears, aging is not a simple problem at the level of physiology. It is instead an extremely complex problem. It is only simple from the standpoint of evolutionary theory, as I have outlined, and, as we will discuss, evolutionary experimentation.

22. Repairing molecular or cellular damage will provide at most partial amelioration for the problem of de-tuned adaptation with adult age, because cumulative damage will also occur at organ and systemic levels at every physiological level as a result of the de-tuning of adaptation with age.

One of the basic theories of aging that has enjoyed popularity among cell and molecular biologists is that aging is due to cumulative damage at the cellular and molecular level. Taking this particular reductionist theory as gospel, the charismatic Aubrey de Grey has proposed that we can solve the problem of aging simply by repairing all such damage. In his somewhat Panglossian view, there are only seven types of cell/molecular damage, and there are relatively straightforward ways to repair that damage, he says. On the basis of this line of reasoning, de Grey expects that a sufficiently concerted research effort should be able to overcome aging within the next thirty to fifty years.

Even if we take this "aging is cumulative damage" theory on its own terms, well-trained pathologists would naturally point out that cumulative damage can also occur at the organ and systemic levels. Those addicted to running assiduously pound away on their joints if they run regularly on concrete and other paved surfaces. After the early twenties, our joints no longer re-grow cartilage, so such running can literally wear-away the connective tissue that sustains joint function, progressively hobbling us. The acids in our stomach frequently reflux up into our esophagi, eating away at their tissues, leading to degraded esophageal function, which we experience as heartburn and difficulty swallowing. And this list goes on.

Damage occurs at every level of our bodily machinery. Yes, it always involves changes to molecules and cells, but the causes of cumulative damage are not confined to those levels. Furthermore, the widespread turnover of cells and molecules throughout much of the human body suggests that our bodies already have fairly good machinery for dealing with damage at these lower levels: get rid of damaged cells and replace them with new ones that have not yet been damaged.

Thus, even on their own terms, molecular damage theories of aging do not necessarily lead to elegant technological solutions to the problems of aging, because there are many types of damage that may require repair, some well above the level of individual cells functioning in isolation.

23. Repairing all types of cumulative damage during the aging phase will provide at most partial amelioration for the problem of declining adaptation with age, because some of this decline will be due to failures of signaling and other features of gene regulation as a result of the de-tuning of adaptation with age.

The functioning of cells as complex as those of humans involves much more than the repetitious execution of the same biochemical processes over and over again. Rather, our cells have elaborate networks of interaction among proteins and the nucleic acids involved in their synthesis. Among the specific agents involved in these complex networks are transcription factors, proteins that affect the production of other proteins, sometimes on a vast scale, with one transcription factor affecting the production of hundreds of different types of protein.

This coordination of function by cells involves intracellular signaling cascades and other information-laden patterns of coordination. In a sense, the human cell is a spectacularly complex hybrid analog-digital computer, where the digital components are provided by the nucleic acids, and the analog components are the proteins. At ages when natural selection is acting with its full power, what our cells can accomplish is remarkable with respect to efficiency and precision. But with an evolutionary view of health and function like the present one, as the forces of natural selection fade with adult age, the control of our cell functions is expected to deteriorate. Thus, we can expect that some of our cells will become so dysfunctionally regulated with age as to turn malignant, losing self-inhibitory mechanisms, and degenerating into highly proliferative rogue cells that engender cancer, to give just one example.

It is not the case that, during aging, perfectly and perpetually attuned cells progressively lose function solely because of a substratum of damaged molecular components. In addition to any such damage, the evolutionary genetic tuning required to sustain the signaling systems of the human cell will not be there at later ages. Metaphorically, it is not just that the car is rusting; the driver is also falling asleep. The cell genome is running out of information with which to sustain its role at later ages. There are any number of metaphors that could be used here: an actor who has run out of script; a videogame that hasn't been properly programmed for its later "levels;" driving away from a city and having its radio stations fade out; and so on.

Thus, whatever damage we are able to repair at the level of cell, there will still be failures of function arising from progressively more severe failures of coordination among the complex networks that sustain cell functions.

24. Altering all cell-molecular regulatory signaling during the aging phase will provide at most partial amelioration for the problem of declining adaptation, because dysfunctional signaling will also arise at organ and systemic levels as a result of the de-tuning of adaptation with age.

The functioning of a whole organism as complex as a human involves much more than the repetitious execution of the same processes over and over again. Rather, our physiology involves a number of signaling pathways among tissues and organs, from the slower hormonal signals to the rapid electrical signal transmission carried out by neurological tissue.

At the peak of adaptation, just prior to the onset of reproduction in an evolving population, this coordination of function by signaling is amazingly proficient. Thus we have the thirteen year-olds with an amazing ability to acquire random new information, whether from friends, the internet, or even their teachers. But with an evolutionary view of health and function like the present one, these gifts are the predictable effect of natural selection operating at full power.

Conversely, as the forces of natural selection fade with adult age, our mental facility and our physiological responsiveness deteriorate. This deterioration is masked in humans by the accumulated intellectual capital and skills that we have acquired thanks to our earlier proficiency at signaling, coordination of functions, and marshalling of resources. Older professors usually know more than beginning graduate students, and veteran athletes know the tricks of the game that the upcoming rookies are just learning. But the reaction times of the professors and the veteran athletes will generally be slower than those of their younger colleagues.

It is not the case that, during aging, a perfectly attuned organism progressively loses function solely because of a substratum of progressively damaged cells or organs. In addition to any such damage, the evolutionary genetic tuning required to sustain the signaling systems of the human body will not be there at later ages. Again, it is not just that the car is rusting; the driver is also falling asleep. To suppose otherwise requires a resort to a Cartesian dualism in which “the mind” and other coordination functions come from another realm, one that is not subject to the lack of information that afflicts the body, considered as an inert aggregate of cells. And I reject any such Cartesian dualism, as I suppose most modern biologists must.

Thus, whatever damage we are able to repair at the level of cell or organ, there will still be failures of function arising from progressively more severe failures of coordination among tissues and organs. Perhaps a useful metaphor for this would the American Congress, which features a lack of coordination that can boggle the mind of the uninformed American voter or the visitor from a country that has a rational legislative system, particularly one not designed to thwart cogent and expeditious policy.

25. Repairing all forms of cumulative damage and altering all types of regulatory signaling during the aging phase will also fail to fully alleviate aging, because some features of aging will arise from the absence of structural gene-products required to sustain health indefinitely during adulthood as a result of the de-tuning of adaptation with age.

But not all failures of adaptation at later adult ages will be due to damage or poor coordination. Sometimes the endogenous deaths of adults arise from the absence of necessary bits of machinery, from the level of the cell to that of the entire organism.

It is at the level of the whole organism that this failure of evolution to supply "missing parts" is most obvious. The rapidly deteriorating adult mayfly lacks mouthparts. Its sole role as an adult is to find a mate, copulate, and, if female, deposit its eggs appropriately. This is also true of many moth species, which also entirely lack functional mouths as adults. Evolution's failure to sustain mouths in some adult insects is a fairly extreme failure to supply a part whose lack dooms them to deterioration and an early death.

With somewhat greater subtlety, vertebrates vary widely in the availability of replacement teeth. Humans get just two sets in their lives. Elephants get six. But in either case, absent dentistry, once we have lost too many of our ultimate set of teeth, our subsequent nutrition will be impaired.

By this same biological logic, there is no reason for natural selection to supply our cells with enzymes that might catalytically prevent or repair sundry types of damage or dysregulation at indefinitely great ages with full efficacy. Evolution will produce biochemical bits of cell machinery that sustain function at every age, if there is no trade-off or separation between these functions at different ages. Worse still, if evolution by natural selection faces a trade-off between earlier and more prolific reproduction and the provision of missing components that might sustain life indefinitely, the declining forces of natural selection combined with this antagonistic pleiotropy will ensure that the later adult will be missing key features required to sustain life infinitely.

26. The forces of natural selection can be strengthened during adulthood by postponing the first age at which they begin to decline, which can be achieved for the force of natural selection acting on age-specific mortality by postponing the first age of reproduction.

Much of the first 25 theses focused on problems with prevailing views. That is, in large measure, to this point I have been setting about the destruction of conventional views concerning aging and the foundations of health, views that dominate Western medical thinking about medicine and cognate health issues.

But this would not be a very useful effort if it were little more than a critique of existing medical or gerontological thinking. Starting with this thesis 26, I will be setting out a positive alternative program, a set of ideas about experiments and health practices that can make a constructive difference to patterns of aging.

Let's start with the first important idea I had as an experimentalist, in the fall of 1977. That was when I realized that the natural selection might quickly retune aging if it was artificially strengthened at later adult ages. A key parameter affecting the force of natural selection acting on survival is the first age at which a population begins to contribute offspring to the next generation. This parameter is conventionally labeled **b.**

Basically, the force of natural selection acting on survival is weighted according to the proportion of a population's reproduction that lies in its future. By increasing the value of **b** in an experimental context, one would be strengthening the force of natural selection at all ages between the previous value of **b** and its new higher value. As a matter of biological practice, **b** can be shifted upward to a much higher value so long as there are enough fertile survivors available after the new first age of reproduction.

This was simple mathematics. But what remained unaddressed in 1977 was whether or not there would be enough standing genetic variation, or "heritability" in the language of quantitative genetics, for natural selection to respond quickly to this shift in the force of natural selection. At that time, we did not know how common such genetic variation was among outbred populations. In particular, many biologists, even evolutionary biologists, thought that genetic variation affecting characters like survival was pretty thin on the ground. That was because they were still thinking in terms of evolution in terms of intermittent, rare, beneficial genes arising by mutation and sweeping toward fixation.

A simple way to understand my career, and my reputation as a scientific rebel – if not rapscallion, is that my success as a scientist has been based on repeatedly betting against conventional wisdom. At times, when I have bet against the conventional

wisdom, I was betting against the very beliefs that I had been inculcated in during my training. Thus, I was often betting against assumptions that I myself cherished, and might have been as unable to question as anybody else just weeks or months before.

27. Among populations which have had their forces of natural selection strengthened experimentally, detectable improvements in adult survival and reproduction have been observably achieved within dozens of generations.

So there I am, in 1977, realizing that all evolution has to do to postpone aging is have its force of natural selection strengthened during adulthood by shifting the age of first reproduction. What was not clear then was whether or not it could do so quickly.

The experimental material I used to test this idea was a laboratory population of the fruit fly, Drosophila melanogaster, which I was maintaining at moderate populations sizes of around 1,000 to 2,000 individuals. Would this population have the genetic variation I needed to test the idea of slowing aging by shifting the age at which natural selection would start to fail?

At that time, I was engaged in laboriously testing that population for its quantitative genetic variation. But I wouldn't get all the results I needed for another 16-18 months. So, impetuously, I just gambled that it would be there. Fortunately, my advisor was away for the year, and couldn't talk me out of this plan. Nor did I have to appeal to a "better not" grant-review panel.

I took that fruit fly population and split it into controls, which were reproduced at 14 days of age from when they were eggs, and an experimental population, which reproduced at 35 days of age. I then maintained these two populations like this for a dozen generations of late-reproducing flies, about a year. Then I reared them in parallel, and observed their pattern of reproduction and survival as adults.

The results were that the population with postponed first reproduction, an increased **b** in Hamilton's terminology, had a significantly increased average lifespan and a shift of reproduction from early to later ages. That is, my bet had worked. In only a year, my delayed-reproduction fruit flies had their pattern of aging evolutionarily shifted toward slowed aging.

Since then, this experiment has been repeated many times by myself and others, with fruit flies, other insects, and even mice, and the results have been qualitatively consistent. Shifting the first age of reproduction upward quickly results in the evolution of increased lifespan and somewhat slower aging. Even with the bad technique that prevails in most biological laboratories, this experiment is easily done, and the results are predictable.

This was the experimental breakthrough that has served as a crack in the edifice of conventional theories of aging, a crack through which the waters of scientific change have seeped ever since. The journals and the grant-reviewing panels have mightily resisted this scientific change, as we can expect that they always will resist substantive

reform of conventional views. But the power of strong-inference science cannot be resisted forever, not even by biologists and physicians, as those of us who are the scientific descendants of Charles Darwin know well. We evolutionary biologists all grow up intellectually on tales of the obdurate stupidity of scientific establishments.

28. Among such experimental populations evolving greater levels of adaptation at later adult ages, evolutionary changes in (a) structural gene frequency, (b) gene regulation, (c) patterns of cumulative damage, and (d) still other features of physiological function will reveal the mechanistic changes required to enhance adaptation at later ages in that species, and thereby ameliorate its aging.

Laboratory populations that have evolved greater levels of adaptation, and thus prolonged survival, during adulthood are key material for unraveling the conundrums of aging. If the views articulated here were NOT correct, it wouldn't be possible for experimental evolution to turn aging around on a dime by delaying the decline in the forces of natural selection. Instead, the nostrums of molecular biologists would readily and easily postpone aging. But they don't. Thus biomedical research on aging should focus on what evolution does when it slows or postpones aging.

So there now exist material embodiments of re-tuned aging: Methuselah Flies that have much greater lifespans, both average and "maximum" (where the definition of the latter is a problem that we will discuss later in the 55), as well as better sustained fertility. As such, we can directly examine just what it takes to re-tune aging, at every level: genetic, biochemical, molecular, cellular, organ, and whole-organism.

My laboratory has already released an entire book on the experimental characterization of how these Methuselah Flies are able to live and function longer (Methuselah Flies, 2004; Rose, Passananti, & Matos, eds.; World Scientific). That would be the work to read for an introduction to these flies.

But let me give a crude overview of what longer-lived, longer-reproducing, fruit flies are like. They have changes at many genetic sites distributed throughout their genomes, NOT changes at just a few genes. This means that genetically engineering or pharmaceutically manipulating human biochemistry to achieve radically greater lifespans is not going to be a feasible project. There are too many targets Instead, our physiologies have to be re-tuned at many levels, and in complex ways.

Some of this physiological complexity is starting to emerge from careful work on fruit flies with improved aging. Here are some characteristic features of longer-lived fruit flies: greater resistance to acute stress, greater physiological reserves, normal metabolic rates, better maintenance of physical activity, greater athletic endurance, greater reproductive restraint under bad conditions, and so on.

A number of molecular biological hypotheses about aging have been tested in these flies. While the failures to corroborate these institutionally favored hypotheses have consistently NOT been published, because at least some molecular and cell biologists exhibit little commitment to strong-inference science, I can tell you that there is

significant unpublished research on these flies which falsifies favored reductionist hypotheses. To a first approximation, it would be fair to say that these flies have served as a nemesis for conventional molecular and cellular theories of aging. Overall, the reductionist theories of aging appear to be systematically worthless, of no better than incidental validity, from the evidence of experimental evolution. Which is just as evolutionary theory suggests they should be.

29. Species with fully symmetrical fission as the sole means of reproduction do not have a declining force of natural selection acting on survival, and they do not evolve aging phases in which all individuals show declining survival.

I have already mentioned that there are organisms that show no signs of aging, not even when they are carefully maintained in scientific laboratories. Some of these are multicellular animals that have eukaryotic cells very similar to our own. Yet, no aging. Ergo, aging cannot be due to features of cell biology that are common among animals.

It is not trivial which animal species evolve to be free from aging. These are all species in which the Forces of Natural Selection do not decline, as is to be expected in the evolutionary theory of aging.

Under what conditions is such decline prevented? As already mentioned, non-aging species reproduce by splitting into similar offspring, only. Coelenterates that reproduce in this fissile manner only do not usually show aging. Other coelenterates that do not have any type of fissile reproduction do undergo aging.

The fundamental determinant of aging is whether the Forces of Natural Selection decline with adult age or not, rather than the biological details. If an organism develops to the point of reproduction, and then reproduction leads to two symmetrical "newborns," there is no opportunity for the Forces of Natural Selection to fall, because there is no adult organism at all. There are only juveniles.

As the Methuselah Flies also suggest, the straightforward evolutionary explanation of the existence of non-aging animals brutally demonstrates the vacuity and irrelevance of the cell-molecular approach to aging, the overwhelmingly dominant biomedical research paradigm in aging and biomedical research.

More generally, it also suggests the vacuity and impotence of the cell-molecular paradigm for systematic progress in addressing most of the key chronic diseases which are devastating millions of people in industrial countries. Cell and molecular biologists will certainly generate many publications as they study such chronic diseases. And they will award each other numerous research grants, get their protégés good tenured faculty jobs, etc. But millions of patients will suffer and die for the scientific and technological inadequacy of the prevailing cell-molecular dogmas. This seems like a high price to pay for continuing to support a biomedical priesthood that chooses to overlook the limits to their knowledge, sometimes willfully.

If Martin Luther was so outraged by the excesses of the Catholic hierarchy that he posted 95 theses on a cathedral door, my 55 theses reflect a still greater outrage over the millions that are now suffering and dying in order that the present-day

complacency of the biomedical establishment, and its allies in the pharmaceutical industry, be maintained without challenge.

30. The forces of natural selection plateau at zero values at very late adult ages, and do not decline further for all subsequent ages.

This is the most important thing of all, even if no one understood what it means for human health for decades. The point is this. Aging is merely the de-tuning of adaptation during adulthood, not a physiological process. This de-tuning arises from the falling forces of natural selection. Ergo, if these forces stop falling, then the de-tuning of adaptation should stop too. This means aging can stop.

Thus the point that the forces of natural selection stop falling is key to everything that follows in the present re-visioning of the prospects for human health. So you need to pay careful attention to this point, because it has the potential to change the lives of billions of people.

A brief detour into the history of physics is possibly instructive, even though I am not expecting you to worry about the details of the physics involved. The hallmark of real science, as opposed to the trivia of natural history and cell biology, is that its equations can have spectacular consequences. Thus the apparently simple equation $E = mc^2$ is one of the most practically important results in all of science, for the following reasons. It gives the relationship between mass (m) and energy (E), when mass is converted into energy. Little noticed by most people, who aren't physicists after all, is the c^2 term. The symbol c in physics stands for the speed of light, which is a very big number. Square it (multiplying it by itself) and you get an even bigger number. This then implies that converting just a small amount of mass into energy will release a great deal of energy. That in turn is what generates the tremendous blast force of nuclear weapons, because they contrive circumstances in which such a conversion of mass into energy happens quickly. From the simple scaling supplied by c^2 comes one of the most portentous technological developments in human history, nuclear weapons.

The result $E = mc^2$ was derived by Einstein and published in 1905. It was part of Einstein's re-structuring of the foundational theory of mechanics, by which the Newtonian tradition in physics was replaced with what is often called "modern physics." Modern physics is both counter-intuitive and devastating in its material significance. If science were like religion or politics, activities which are guided by what is intuitively comfortable rather than true, modern physics would have been sternly rejected by the physics community, and Einstein's 1905 papers would never have been published.

In this respect, conventional gerontology, and much of the cell-biological community which underpins medicine in our time, operates like religion or politics, not like physics. Most gerontologists and most cell biologists don't even want to think seriously about the implications of equations like Hamilton's forces of natural

selection; they aren't scientists as physicists would use the term. They are more like creationists than they will readily admit; their views have more to do with what they find comfortable.

The mathematical result that the forces of natural selection eventually plateau implies that aging can come to a stop, which is as portentous for health as $E = mc^2$ has been for warfare, as will be explained in detail in subsequent theses. But the biomedical research establishment doesn't want to deal with this; they would rather their cell-biological thinking go unchallenged.

31. After the forces of natural selection plateau, it is possible for survival and reproduction to plateau at positive values due to age-independent beneficial effects of some genetic variants.

As with modern physics, again, it is often difficult to intuit how the evolution of health and function will proceed. The possibility that the eventually plateaus in the forces of natural selection implied that aging might stop was not appreciate by Hamilton in 1966 when he first published their derivation. Nor was it appreciated by Charlesworth during the 1970s, in the course of his decade-long development of the detailed evolutionary genetic theory which underpins the use of Hamilton's forces in evolutionary genetic research. Nor was it appreciated by myself during the course of 15 years of research in which I deliberately re-tuned Hamilton's forces in the laboratory, using experimental evolution of fruit flies, from 1976 to 1991.

Indeed, it wasn't until evidence started to accumulate that our interpretation of these equations was erroneous that their implications were re-examined. Though I am somewhat chagrinned about this, it is a common enough situation in genuine science. Modern physicists, including Einstein, often didn't realize the full implications of their own equations, at least not at first. Thus a significant part of the history of physics in the 20th Century involved the slow discovery, often stimulated by bizarre experimental results, of the manifold implications of the mathematical equations on which it was based. The same thing is true of evolutionary genetics, the most physics-like part of biology.

In any case, evolutionary biologists have now developed formal analyses of the implications of the plateaus in the forces of natural selection for the evolution of health and function. One of the most elegant was supplied by Charlesworth himself in a 2001 article. The result is simple enough that I will try to explain it verbally here.

Separate in your mind age-specific genetic effects from age-independent effects. Age-specific effects are illustrated by genetic disorders like Huntington's Disease, which starts to damage the central nervous system of people chiefly in their 30s, eventually causing death a decade or two later. Then there is Familial Alzheimer's Disease (FAD), which is a genetic syndrome that causes Alzheimer's Disease in middle age. On the other hand, some gene substitutions can have beneficial or deleterious effects across a wide range of ages. Sickle-cell anemia has adverse effects on blood circulation starting in infancy, and continuing through the rest of life. Thus, conversely, having the normal gene for hemoglobin has benefits throughout life.

If individuals do not die because of adverse environmental conditions AND do not die because of age-specific genetic effects, they will survive through the aging period to reach a post-aging phase of lowered but sustained survival, thanks to age-independent genetic benefits produced by genetic variants favored at all ages by

natural selection. There is no guarantee that this will always happen, but the equations of evolution by natural selection allow it to, especially when animals are supplied particularly good conditions in which to live.

32. Before the forces of natural selection plateau, it is possible for genetic drift, due to small population sizes among other possibilities, to weaken the ability of natural selection to distinguish among genetic variants affecting later adult life, leading to the evolution of even earlier plateaus in survival and reproduction.

But there are still other factors at work in the evolution of the cessation of aging. One of the most important of these is the role that population size can play in determining the window of adult ages over which natural selection is effective. This finding was discovered by Larry Mueller during his numerical studies of the implications of age-specific selection for the evolutionary transition from aging to later adult life. [See the Mueller and Rose (1996) article, listed in the bibliography.]

As mentioned before in the 55, there are a number of factors that serve to limit the power and efficacy of natural selection. One of the most important of these is the number of breeding individuals in a population, what is called the "effective population size" in evolutionary theory. Effective population size is quantitatively complicated, but basically it can be understood as the number of individuals who are contributing genes to the next generation. This concept also has age-specific quantitative features. In particular, the forces of natural selection are further attenuated with adult age in finite populations, compared to their theoretical power in populations that are infinitely large.

To give you some idea of what this means in human terms, the present human population size is about 7 billion people, with an effective population size of about half that, somewhere around 3 billion. At such a large effective population size, there is little attenuation in the forces of natural selection due to population size. But in our ancestral condition, prior to agricultural, we had a much smaller global population size, and we were split up into separate breeding groups, further reducing the effectiveness of natural selection, at every age.

Larry Mueller's computer analysis shows that such small effective population sizes will lead to the evolution of much earlier mortality plateaus. Thus, in human terms, hunter-gatherer populations probably evolved mortality plateaus somewhere in their fifties or sixties, rather than the eighties or nineties that appear to be the case for agricultural populations on organic agricultural diets. In this respect, our ancestors were probably more like many other large mammal populations, especially mammalian predators, which rarely achieve the large population sizes of either widespread rodents, like rats, or ungulates, like caribou or bison, prior to European colonization of North America. Thus, thanks to the limits on their past population sizes, hunter-gatherer populations living their ancestral lifestyle probably undergo much earlier plateaus in their mortality rates, compared to agricultural populations that have risen to much higher population sizes, with greater efficiency of travel between populated

areas. Thus European, Middle Eastern, and other Asian populations have probably had prolonged aging relative to that of non-agricultural populations, simply because of the much large population sizes of the former group. Or at least they probably do when subjected to the agricultural conditions under which the former group have evolved over the last ten to twenty thousand years. More on this later.

33. When late-adult plateaus in survival and reproduction occur, members of biological cohorts that reach such plateaus will show stabilization of some but not necessarily all functional characters.

Evolutionary theory makes a simple prediction about how the key characters of our life history evolve at very late adult ages: they should tend to plateau. These plateaus aren't necessarily precisely flat, but they are expected to be very different from the rapid deterioration shown during the aging phase.

During the aging phase, sooner or later our functions deteriorate. Some of these functions deteriorate glacially in humans, with our relatively slow pattern of aging overall. But other functions decline with remarkable speed. This is shown most publicly in the short careers of track-and-field athletes and gymnasts, who may be essentially non-competitive at the world level by the time they reach their early thirties.

After aging comes to a stop with respect to survival and reproduction, what of these subordinate functional characters? There are two broadly conceivable possibilities. One is that all these functional characters will show slowing rates of decline, gliding toward to a reduced but steady level of useful function. The other is heterogeneity among these functions, with some continuing to decline, while others stabilize or even improve.

Early data collected by my graduate student, Parvin Shahrestani, suggests that the latter is the case: after aging stops in aggregate life history, individual functional characters show some variation in their pattern of change. Some stabilize, and perhaps may rise slightly. Others continue to decline, sometimes at a slower rate. Finally, and amazingly, some functional characters actually decline at a faster rate after mortality rates have stabilized.

There are some hints that this is the human case as well. For example, there is no sign that wrinkling abates with age. Indeed, it appears to be the case that the tissue matrix of our skin accumulate wrinkles largely as a function of the movement of our skin and its exposure to sunlight, desiccating wind, etc. But consider memory. One of the characteristic symptoms of human aging is a declining ability to acquire new names for people, animals, and places, terms that have no reliable semantic pattern. On the other hand, some very old people develop a remarkable ability to recall events of their early lives, often in considerable detail. What may be occurring is that some functions may interfere with each other, such that the decline of some may lead to the reinvigoration of others. Thus, perhaps, as we lose our ability to acquire new "random" terms and facts, our access to more meaningful memories is enhanced?

Evidently, there is much to be learned of the patterns of functional change in the post-aging phase of life, both in experimental animals and in clinical patients. But the idea that late adult life is always a period of universal functional stability is not correct.

34. Severe antagonistic pleiotropy can cause the evolution of zero late-adult survival probability even under ideal conditions, when genetic trade-offs between early reproduction and subsequent adult survival are sufficiently strong.

Not all organisms have three phases to their lives, with development, aging, and late life following each other in order, when they are protected by humans from the deadly slings and arrows of life in the wild. Some have life cycles with just two phases, regardless of how well we take care of them. In these cases, development is followed by a brief and tumultuous adulthood, characterized by an unremitting focus on reproduction, leading to an early death. That is, nature has its share of tragic young "shooting stars," species that exhibit neither protracted aging nor a post-aging phase of relative stabilization, when kept under good conditions.

This is a common pattern among annual plants, which die shortly after their flowering. Among invertebrates, it is famously the pattern of mayflies, which may have an adult phase that lasts just hours. Less famous are the many moth species that emerge from pupal cases without mouthparts, spending their brief adult lives seeking mates and dying shortly after the females lay their eggs. The Pacific salmon are well-known for their strenuous and brief adulthood, spent swimming upstream to their natal streams. On reaching their destination they furiously spawn, and quickly die, over the course of days.

Yet some of these species can be given protracted lives by the simple expedient of castration, as already mentioned. Pacific salmon can thereby lives for years longer, in laboratory aquaria, after careful excision of their gonads.

What is occurring here is that antagonistic pleiotropy between early reproduction and subsequent survival is so severe that later survival is entirely precluded if the physiological mobilization for reproduction is allowed to occur. There is nothing about the workings of evolution by natural selection that is solicitous for the survival of the adults of any species, if that survival impinges on the net rate of transmission of genes into the next generation. This "gene-level" view of what natural selection provides in turn explains many paradoxes in biology: the sterility of worker honeybees, the male praying mantis allowing his mate to devour him, and the attenuated adult lives of the "big-bang" reproducers of the plant and animal worlds. Thus, from an evolutionary standpoint, the Dionysian rock-star who has many sexual conquests and a short lifespan is not necessarily the tragic failure that those of us with more pedestrian lifestyles might think, at least evolutionarily.

A protracted aging phase followed by a distinct late life phase is not a necessary product of lifecycle evolution. It is merely one of several possible life cycles, along with big-bang suicidal reproduction and a fissile life cycle with no aging whatsoever.

Evolution by natural selection rules the shapes of our lives, with an unremitting force that defines what the limits of our lives will be, absent radical medical intervention. Castration, awkwardly enough, shows the extent to which such drastic interventions can surmount evolution limitations. While I am not in the business of recommending castration, my point would be that it does show the promise of what we might eventually attain using different means.

35. The ages at which the forces of natural selection plateau depend on the last ages of reproduction and survival in the evolutionary history of a population, allowing experimental evolution of the cessation of aging by deliberately changing those last ages in laboratory populations.

Earlier in the 55, it was pointed out that it proved relatively easy to manipulate the evolution of patterns of aging by the simple expedient of changing the first age of reproduction in laboratory populations over a number of generations. This was the means by which the creation of Drosophila populations with slowed aging became a routine experiment of aging research.

My intuition in the 1990s was that changing the last age of reproduction in a laboratory population would change the age at the aging phase comes to an end, over the course of evolution. So I persuaded Larry Mueller to simulate the evolution of populations which were subjected to such a change in their conditions of evolution. As I had hoped, my intuition was correct: changing the last age of reproduction or survival in a population's life cycle eventually leads to the evolution of corresponding changes to the timing of the cessation of its aging. Specifically, populations with a later last age of reproduction evolve a later cessation of aging.

As it happened, my laboratory had a spectrum of Drosophila populations that had undergone evolutionary shifts in their last ages of reproduction over hundreds of generations, so it was relatively easy to check whether or not the ages at which their aging ended had shifted in the expected manner. Briefly, what we actually found in our populations qualitatively corresponded to what Larry Mueller's numerical simulations had predicted: fruit fly populations which we cultured for hundreds of generations with an early cessation of reproduction during adulthood had an earlier cessation of aging, relative to populations with a later cessation of reproduction.

What this showed was that evolution readily tunes the cessation of aging according to the forces of natural selection, just as it tunes the rate of aging. There is nothing difficult, for evolution, about changing when the aging of a species stops.

So we went a step further. We tried changing the age at which reproduction ceased over just a small number of generations, about twenty. To our surprise, the age at which aging stopped then evolved even faster than the rate of aging evolved. It is as if there is much less evolutionary friction affecting the cessation of aging than the rate of aging. In principle, this implied that changing the point at which our aging stops might be an easier project than changing our rate of aging.

However, when we wrote up this result for publication about ten years ago, we still didn't realize how easy it would be change the point in an animal's life at which aging stops. But more on that later.

36. Experimental populations which have evolved different time-points for the cessation of aging can be used to uncover the biological foundations that determine the timing of the cessation of aging.

During the 1980s and 1990s, my laboratory devoted a significant proportion of its efforts to working on the biology of fly populations that had slowed aging. Many of these studies are gathered together in the book Methuselah Flies, which came out in 2004. We deliberately left our research on the cessation of aging out of that book. So what the book reflects is our attempts to study the kind of physiological changes that are involved in making a fruit fly age at slower rate. One of the surprising things about that research was how basic or elementary the changes involved were, from the standpoint of physiological subtlety. The issues that are important to fruit fly aging, as far as the flies themselves are concerned, involve whole-organism attributes like the allocation of fats between survival and reproduction, the extent to which flies hang on to their water reserves, and so on.

Similar studies can be made of flies that have different time-points at which aging stops. One of my senior graduate students as of this writing, Parvin Shahrestani, is now studying the whole-organism physiology of both aging and the cessation of aging in fruit flies that have very different ages for the cessation of aging. We don't yet know what her results are going to look like, but the experimental project itself is relatively straightforward.

There is no reason why we cannot figure out the physiology that lies behind such shifts in aging and its cessation. All my laboratory lacks is the resources to make the study of this question more intensive than we have managed to this point, the natural result of getting too far ahead of our colleagues on the panels of granting agencies.

In addition to Parvin Shahrestani's whole-organism research, we have an early view of the genomics that underlie wholesale shifts in patterns of aging and its cessation. This was the work of my graduate student, Molly Burke, published in the journal Nature in September 2010. Her work shows that many genes may be involved in shifting patterns of aging and its cessation. Thus, at the molecular level, the foundations of transforming aging and its cessation are quite complex.

It will take some time for the biological research community to establish the specific genetic and physiological mechanisms that can be used to slow aging and to stop it. Fortunately, as we will now discuss, we have recently discovered some exciting short-cuts that might provide us with partial solutions. These can be thought of initial down payments toward the detailed genome-wide, cell-wide, and organism-wide findings with which we will eventually fully decode the complex networks which underlie aging. But I think that you will find them promising nonetheless, as you work through the rest of the 55. These short-cuts involve environmental manipulation. Thus the 55 now

turn to the biology that underlies not the evolution of aging or the evolution of its cessation, but instead the biology that underlies the effects of environmental change on aging and its cessation.

37. Patterns of aging, including the rates of decline of functional characters and the timing of any cessation in such decline, depend on the environments in which cohorts are raised and live as adults.

One of the commonplace results of aging research is the increase in lifespan that occurs when animals are given qualitatively good nutrition, but deprived of as many calories as they would consume ad libitum. As we have already discussed, this is a natural outcome of the cost of reproduction, because diminished diets, either quantitatively or qualitatively, typically shut down reproduction. With the curtailment of most or all reproduction, survival then benefits, providing there is no acute starvation.

But there are more general principles to be appreciated than this one. As we have already discussed, what natural selection accomplishes is a reflection of the previous environments an evolving population has been subjected to. Differences among these environments may involve more than quantitative levels of calories and other nutrients. Some environments are qualitatively different.

Such qualitative differences can then lead to major differences in life history, with significant changes in development, aging, and late life, after aging ceases. In particular, a sufficiently novel or toxic environment may lead to a lack of the age-independent adaptation required to allow a post-aging phase in which reproduction and survival are sustained.

Recent experimental work in my laboratory led by my present graduate student Marta Santos has supplied the following Drosophila results: (i) some evolutionarily novel environments lead to long-sustained aging phases, with late life either shifted to much later ages or entirely obliterated; (ii) adaptation to one environment can change aging in another environment with respect to both the rate of that aging and the timing at which it eventually ceases.

These experimental findings suggest that there is nothing absolute or environment-independent about patterns of aging, including its rate and the timing of its cessation. This raises the possibility that there may be environments in which human patterns of aging might be systematically different. As I will argue below, there may be ways of life which, if adopted by men and women, might entail significant slowing of their aging, as well as fostering its cessation.

38. Some environmentally-induced variation in patterns of aging reflects the impact of selectively-favored patterns of life-history plasticity, but some environmental variation in aging does not reflect adaptive plasticity, such as that due to novel environments.

An important distinction needs to be drawn, in light of the findings just mentioned. This distinction revolves around differences in the ways environments impinge on aging.

When aging in mammals or insects responds to reduced nutritional levels, in at least some cases these responses reflect selectively favored forms of plasticity. Drosophila, the fruit flies that I work with, have a number of molecular signaling mechanisms which regulate reproduction and other aspects of their metabolism in response to diet. This is not to claim that there aren't direct effects of nutritional changes on fertility, physiologically. There certainly are: if an animal doesn't have the fats, amino acids, and other substances required to build eggs, then those eggs won't be made, and that animal won't reproduce. But there are also well-known signaling pathways involved, such as those that involve genes like sirtuins and the daf loci. Such signaling pathways produce adaptive plasticity, plasticity which on average enhanced Darwinian fitness in the evolutionary past of these populations.

But other forms of physiological change, and thus resultant changes in patterns of aging, do not necessarily involve either adaptive plasticity or allocation of nutrients. These changes in aging patterns arise from animals being exposed to compounds that they may lack useful responses to, compounds that do not engender well-defined or well-regulated physiological responses. The point is that evolutionary novelty can place animals in settings for which they simply lack the adaptations required to cope.

This is what humans are now doing to many animal and plant species, including ourselves. Our chemists, both pharmaceutical and industrial, are rapidly developing and releasing chemical compounds which are largely or completely novel. Such novel compounds establish environments, and concomitant physiological effects, that evolution by natural selection has not molded contemporary living species to cope with. Under such evolutionarily novel conditions, our bodies do not have the physiological or even anatomical equipment to function with high levels of fitness. That is, industrial foods, cleaning products, fabrics, and the like can be expected to systematically degrade our function, when everything else is equal.

An important exception to the problematic nature of pathological novelty is when such evolutionarily novel compounds are used against our disease organisms, be they viral, bacterial, or fungal. Hitting bacteria with a new antibiotic can stop them from damaging, or even killing, us during the course of bacterial infections. Likewise for antiviral and antifungal compounds. Indeed, the two tasks that pharmaceuticals are

best at are: (i) killing things, most usefully our infectious agents; and (ii) knocking out basic physiological functions, such as pain sensation, consciousness, mucous production, or defecation. That is, pharmaceuticals are often effective at shutting down the sensitive networks that sustain life-forms, be they the networks of our pathogens or ourselves.

39. Patterns of adaptation are jointly determined by long-antecedent evolutionary patterns of natural selection, mutation, and inbreeding, as well as the immediate impact of environmental manipulation.

In studying the aging phase and other patterns of adaptation in an experimental organism, or in considering our own patterns of adaptation, we are confronted with a host of impinging factors. From the start of the 55, we have paid attention to the key role of natural selection. This then led us to emphasize the key constraints shaping what natural selection can accomplish, including mutation and inbreeding, but also the declining forces of natural selection during the adult years.

But the additional considerations that have just been outlined also reveal that overlaid on top of whatever evolutionary adaptations a population possesses will be the environment in which that population lives. This can be put in a relatively simple way. There is no such thing as "AGING," considered as some kind of absolute process of deterioration, independent of environment.

Instead, there are different patterns of deteriorating early-adult adaptation which individuals from a population with evolutionary age-structure will show at particular points in its evolutionary history, and in particular environments. Adaptation is fundamentally a transitory thing, dependent on prior evolutionary history, and dependent on the environments in which organisms now live. As aging is merely this age-specific deterioration of adaptation during the first part of adulthood, it is just as affected by prior evolutionary history and present environmental conditions as adaptation in general.

Such effects are very dramatic in the commonly studied experimental organisms, like fruit flies and nematodes. Giving them novel foods or changing the ambient temperatures of the laboratory vessels in which they are maintained can produce radically different results with respect to rates of aging and the timing of its cessation, where "rates of aging" means the rate at which adaptation deteriorates, NOT the rate at which at a hypothetical physiological process of aging unfolds.

But as we too are products of evolution, these strictures apply to us just as much as they do to our experimental organisms. This is what is particularly promising. Those who study aging are slowly becoming convinced of its tremendous plasticity. If I may be a bit self-referential here, throughout my 35 years of experimental research on aging, I have been surprised again and again by how readily aging changes, both in response to experimental evolution and in physiological response to environmental change. Properly exploited, such plasticity offers the possibility of greatly ameliorating human aging, if only we could figure out how best to take advantage what our evolutionary history has made us. It is on this front that the 55 theses offer the most immediate promise for human welfare. But in order to get to that promise, you first

have to realize how little value there is to be extracted from non-evolutionary strategies and findings in aging research. You have to be particularly clear about this because non-evolutionary researchers are likely to reject the promising news on offer here, and they will further attempt to distract with a barrage of spurious arguments. Such intellectual gesticulation and obfuscation is common enough in science; it is just regrettable when it leads to shortened or straitened lives. Do you really want to suffer or die for sake of the intellectual limitations of defensive scientists?

40. Experimental strategies for the study of aging that involve the introduction of novel mutations or increased levels of inbreeding will systematically impair the scientific study of aging, as they degrade and disrupt adaptation generally.

At this point, having got this far into the 55, my hope is that you are ready for the demolition work required to clear some space for the transformation of human aging. This isn't going to be pretty for the holdovers from twentieth century biology. But just imagine how the Aristotelian physicists felt about the physicists who followed Galileo.

To this very day, cell and molecular biologists busily construct large-effect mutants using the Frankenstein technologies that are now available to them, including genetic engineering, cloning, and all the rest of it. Characteristically, they do these things to haplessly inbred organisms that have been maintained with high levels of inbreeding in evolutionarily novel, if not seriously cruel, laboratory conditions. This is The Island of Dr. Moreau of H.G. Wells industrialized on a massive scale, across thousands of laboratories throughout the industrial world.

I do not wish to suggest that this work is valueless. Basic features of the molecular machinery of life have been worked out such methods. Many of those who work on "the aging process" do so in the sincere, if misguided, hope that aging will prove to be a well-defined bit of molecular machinery, perhaps the progressive attenuation of telomeres at the tips of our chromosomes, as already mentioned. Thus this type of experimental research is profitless when it is applied to the puzzles of aging, because aging is NOT a physiological process, as such.

Instead, because aging is solely an age-dependent pattern of failing adaptation in adults, it must be studied using methods that do not systematically degrade the adaptations of the organisms undergoing experiment. Aging should not be studied using inbreeding, massive mutation, or teratogenesis (which means the induction of developmental monstrosity), whether that teratogenesis is achieved surgically or biochemically. All of these interventions systematically degrade adaptation. They will only adventitiously reveal much of the physiological or genetic underpinnings of adaptation. I have already mentioned the best example of a Frankenstein experimental strategy that can reveal aspects of adaptation: castration. But such procedures chiefly reveal only one of the most elementary features of the evolutionary biology of adaptation, and thus aging: the cost of reproduction.

But as a general rule, the best methods for studying aging will be the best methods for studying adaptation. Here are some of the features of such research, at its best: the use of outbred populations and cohorts when studying species that do not normally inbreed as part of their life-cycle; the careful examination of segregating genetic variation in such populations and cohorts, with respect to its abundance and its effects

on the functional attributes of the organisms under study; forestalling developmental disasters, such as those of laboratory-induced teratogenesis. In effect, these rules simply mean trying to study aging in organisms that are not being ill-used.

41. Experimental strategies for the study of aging that involve the use of environments that are evolutionarily novel will systematically impair the scientific study of aging, as natural selection will not have previously fostered adaptation to such novel environments.

In thesis 40, my focus was on the problems created by the Viktor Frankenstein experimental methods of the cell and molecular biologists studying aging. It is my hope that you find this point relatively obvious by this point in your reading of the 55. Here, in thesis 41, I am turning to a more subtle problem, which is that of evolutionary novelty.

An experimenter may go to a great deal of trouble to supply a population of animals with benign conditions, and furthermore forswear the use of unnatural inbreeding and mutagenesis. But there may still be a problem facing their research: giving the study organism a novel environment.

Let's make this simple. Let's say that you are studying aging in cats. You have a large colony of these predatory felines, so many that there is relatively little inbreeding. You ensure that they are kept free of epidemic infection, and of course they are not subjected to competition with other predators, such as dogs, bears, or lions. But you feed them some type of cereal-based "chow," without meat of any kind. This chow contains all the essential amino acids, vitamins, minerals, and carbon sources required to sustain mammalian life, as far as biochemists are concerned.

But it is still the "wrong" environment. Cats didn't evolve to eat cereal-based chow. This cereal-based food will contain substances that cats don't normally digest in much abundance, such as omega-6 fatty acids. Furthermore, the cat gut isn't adapted to digesting cereals in large quantities. Instead, its gut is well-adapted to eating raw animal parts, from muscle to liver.

In this evolutionarily novel environment, cats will suffer an aberrant pattern of adaptation. When they are young, their standard mammalian adaptations to consuming milk may provide them with digestive enzymes and gastro-intestinal function sufficient to allow them to grow and reach sexual maturity while eating this chow. But as adults they will lose most of those functional capacities, and their gut will have developed in such a way that animal flesh will be its ideal food. From that point onward, a cohort of adult cats given such food in your research facility will suffer from BOTH progressive reduction in function arising from Hamiltonian aging AND progressive chronic impairment arising from life under conditions to which it was never adapted. There will thus be TWO sets of worsening pathophysiologies. Sorting them out will be an extremely daunting task, even for an accomplished biologist.

Instead, the better experiment would be to feed these cats their evolutionarily optimal mice and other small prey, particularly if these prey are live and need to be hunted. Of course it seems cruel to us, from the standpoint of the mice. But that is the way of life to which cats have adapted, not some industrial-grade chow.

42. As a pattern of age-dependent adaptation, aging and the post-aging period are best studied using the range of methods used to study adaptation by evolutionary biologists, such as the comparative method, experimental evolution, and genomics.

By this point, you are either open to the idea that aging is only a pattern of age-dependent adaptation or you are going to return to reading articles about free radicals and telomeres, putting the distractions of Hamilton, Charlesworth, and Rose aside. Creationists can comfort themselves by reverting to Bible study, after all, shutting their minds off from the babble of scientists.

So, if you fall into the former group, what is the way forward for research on aging? What, practically speaking, should biologists interested in aging do with themselves, and their laboratory research?

They have to get re-trained as evolutionary biologists. Some of my best gerontological colleagues, such as Caleb Finch and George Martin, have in fact gone some distance down this road. They realize that they need to re-cast their research in terms of evolutionary biology.

Unfortunately, this re-casting cannot be post hoc or superficial. The problem is that the basic intellectual equipment of cell biology is profoundly deficient, from core scientific theory to the tricky articulation of the connection between useful theory and key experimentation. Cell biologists would like to find elegant pathways connecting specific molecular substrates with well-defined pathophysiologies of aging. This is what generates their attraction to free-radical and telomere theories of aging.

But they have to give up on this pattern of thought. For the underlying machinery of aging is that of evolution by natural selection, especially the ways in which it fails to sustain function. It is tricky enough to figure out how natural selection successfully sustains function. It is still harder to study how it doesn't do so.

But this harder problem can nonetheless be approached using the tools that evolutionary biologists use to study adaptation. Among these is the comparative method. Here the beauty of the Hamiltonian theory of aging is that it makes some absolute comparative predictions, such as the absence of aging when the forces of natural selection don't fall because of symmetrically fissile reproduction.

At the other extreme is genome-wide characterization of the genetic foundations of adaptation. This new technology is revealing the many loci that underlie both adaptation and failures of adaptation. And it is from looking at the depth and breadth of such genome-wide data that the challenge facing modern biology becomes clear: underlying any particular organismal function will be hundreds of genes which interact with each other in complex networks. The notion that we are likely to discern how

these networks operate using the reductionist ideas and methods of 20th Century biology is remarkably hubristic. It reminds me of the attempts that the Taoists made to work out the foundations of human health, particularly during the first millennium CE. Despite their great ingenuity, the Taoists were much too far from having adequate conceptual or laboratory resources for the task.

43. Experimental manipulation of the forces of natural selection is one of the most powerful methods of studying the biological foundations of aging, because it can direct experimental evolution to produce extensive genetic differentiation with respect to both the rates of aging and the cessation of aging.

Though there are a variety of ways in which evolutionary biologists can usefully study aging, there is one that is central. That is the use of experimental evolution to produce extensive differentiation in patterns of aging, with respect to both rates of decline in age-specific mortality or fecundity as well as the cessation of such declines. Experimental evolution of aging has been achieved with many populations from the genus Drosophila, as well as on a lesser scale in other species, including the laboratory mouse.

The reason why this particular experimental paradigm is so important is that it can be used to generate well-replicated material to which the full armamentarium of biological research can be applied. Here is what has been accomplished with Drosophila populations with experimentally evolved differences in aging: (i) extensive tests of the basic Hamiltonian theory for aging; (ii) tests of the alternative evolutionary genetic mechanisms that might underlie the Hamiltonian evolution of aging; (iii) extensive characterization of the aggregate physiology of slowed aging; (iv) initial characterization of the physiological transitions involved in the cessation of aging; (v) genetic and whole-genome characterization of the molecular genetic foundations for aging. Some, but by no means all, of this work is summarized in the book Methuselah Flies.

Much more work of this kind could be done with experimentally evolved populations of Drosophila, but of greater interest would be a comparably extensive project using a small mammal. This is because we are mammals. If we are to acquire extensive and detailed information about the functional genomic foundations of our aging, a readily bred and housed mammal would be the best system with which to do so. I spent fifteen years arguing for such work, from 1984 to 1999. Over the last decade, I took a break from this mission to focus on the demographic and genomic extension of my work with fruit flies. But now that we know how effectively genomics can be applied to products of experimental evolution with very different rates of aging, I am all the more convinced of the salience of pursuing similar research with mice or some other readily maintained laboratory mammal. Naturally, this work should be conducted with all due care where potential artifacts and problems are concerned, such as inbreeding and the use of overly novel environments. But it has been relatively easy to apply experimental evolution to the problem using fruit flies; properly designed and replicated mouse studies could yield results of much greater medical significance, even if they are

unlikely to be of comparable scientific value given they cannot be carried out on the same scale as the Drosophila work.

But while we are waiting for the results of such a necessarily protracted mouse evolution project on aging, the question remains what evolutionary thinking can offer us as a means of ameliorating our aging immediately. The remainder of the 55 turns to this challenging question.

44. Most of our ancestral hominin populations of the last million years benefited from increased forces of natural selection at early adult ages under conditions of relatively abundant nutrition derived from hunting, gathering, and cooking and an increased ability to defend themselves against predators, which led to the evolution of relatively slow rates of aging among humans.

We have already discussed possible causes for the wide variation between species in their patterns of aging. Animals that have good protection from predators, such as shells or rapid flight, have slower rates of increase in their adult age-specific mortality when studied under protected conditions. This is because they have evolutionarily benefited from a slower fall in their forces of natural selection, due to lower death rates in the wild during their previous evolution.

The hominin lineage that led to the evolution of contemporary humans had similar benefits. We now exhibit much slower rates of increasing adult age-specific mortality compared to most other terrestrial mammals, even when we protect these other species in zoos, supplying them with food and veterinary care. In this respect, we are like elephants and whales, which are also notably long-lived. This raises the natural question: what was our distinctive adaptation that gave us lower death rates in the wild?

The answer to this must lie in our adoption of proficient tool use and extensive social cooperation. For much of the last million years, we have been a hunting animal that used sharpened stone at the tips or cutting edges of our weapons and other tools. An armed group of us can easily defend ourselves against marauding predators, particularly when we throw spears and fire arrows, as such use of weaponry reduces the need to directly engage a potential predator. This doesn't mean that we were never successfully carried off by the occasional lion or tiger. Solitary adult humans who are caught unaware can still be successfully attacked from behind by large carnivores, as can children. But in armed groups we have long been relatively impregnable to attack by other terrestrial animals.

In addition, we are omnivores who extensively prepare our food, both cleaning and cooking it, as needed. This has given us the ability to eat a wide range of foodstuffs, from practically any animals of significant size to a wide variety of plant parts, from fruits to tubers to nuts to seeds.

Finally, we have a much greater ability to anticipate dangers than other animals. And we share knowledge of such hazards socially, thanks to language.

All these features of human ecology produced a general lowering of our adult death rates even before the advent of agricultural civilization. For a very long time, our

principal mortality risks have been contagious disease, physical accident, and violence toward each other. Perhaps our greatest danger was our fellow man. Contrary to certain Edenic myths, homicide and tribal warfare are common enough among hunter-gatherer populations that have not been conquered by civilized nations.

45. Our ancestral hunter-gatherer populations had generally low population densities, and thus low effective population sizes, which produced relatively early cessation of aging at relatively high function due to genetic drift.

With very low population densities among our ancestors, the effective population sizes of hunter-gatherers was probably much lower than the total census population size of our species. Without question, the total human census population size has been growing since agriculture was first adopted. Coupled to this have been progressive improvements in transportation, making it possible for humans to travel hundreds of miles in their lifetimes thanks to the roads and waterways of agricultural civilizations. Thus, overall, the effective population sizes of hunter-gatherers were substantially lower than that of civilized human populations.

This, by itself, leads to the evolution of an earlier age at which aging stops, as already discussed in these theses. The point is that smaller effective population sizes are subject to less evolutionary "reach through" to higher chronological ages. This means that the forces of natural selection are further weakened at later adult ages, allowing an earlier cessation of aging. This is a numerical result derived from formal theory, so expect to find it relatively hard to intuitively assimilate.

There are present-day human populations that have lost hunter-gatherer patterns of demography and selection only in historical times, in such remote areas as upland jungle New Guinea for less than a century. Among such populations, aging is likely to cease during the age-range that we refer to as "middle age," perhaps between 45 and 65 years of age. Thus, if such individuals were given regular access to food and good quality medicine, yet continued to sustain hunter-gatherer patterns of activity and feeding, they could enjoy long-sustained lives of reasonable health. At least until they die of homicide or the attack of a large carnivore.

That is, among present-day humans, there are some populations that, if they combined their ancestral hunter-gatherer lifestyle with the medical and law-enforcement benefits of modern civilization, could sustain function for many more decades than those of us with agricultural ancestry can. This possibility is strongly suggested by the epidemiological data that Steffen Lindeberg compiled in his 2010 book, "Food and Western Disease." The indigenous populations that he has studied show remarkably low rates of chronic age-associated disease, from cardiovascular disease to cancer to diabetes. At least that is there pattern so long as they do not adopt a Western diet.

When these hunter-gatherer-ancestry individuals adopt Western diets, they show a pattern of age-associated disease at least as severe as that of Western populations leading a Western lifestyle, and often more so. The obvious evolutionary prescription

that can be derived from the 55 is that these individuals should revert to their ancestral lifestyle, at least with respect to diet and activity. Lindeberg presents case-studies where this has been done, yielding a remarkable improvement in chronic health conditions among such individuals. This would be analogous to shifting cereal chow-fed cats back onto their normal diet of animal prey. Animal species will live longer on diets and activity regimes to which they have long adapted, humans included.

46. In the last ten to twenty thousand years, some human populations adopted extensive agricultural cultivation of grass species and the use of milk from other mammals for nutrition, a novel environment which changed the action of natural selection among populations in Eurasia and elsewhere.

But the majority of humans now living come from ancestries in which agriculture has been the normal source of food for some hundreds of generations. Furthermore, associated with this dietary transition has been a change of lifestyle to one which features much less roaming about the landscape. Instead of frequent travel across a wild landscape, settled human civilization has featured relatively sedentary occupation and use of small plots of land, chiefly organized around villages that involve fixed habitation.

From an evolutionary biologist's perspective, evolution took a hunter-gatherer species and initiated a large-scale experimental evolution project, in which most of our species was selected to adapt to a novel regime of diet and activity. Instead of diverse foods, including a fair amount of animal body parts, agricultural populations have been eating diets in which the seeds of grasses and, in some cases, the milk of other mammals have been our nutritional staples. This is one of the most abrupt shifts in nutrition undergone by any species known to us in the history of biological evolution.

This is not, however, the first such shift in hominin evolution. Around three to five million years ago, current evidence suggests that we began to dig up, clean, and cook the underground storage organs of plants, such as tubers and roots. At this point in our evolutionary history, we began to evolve amylase genes that have since helped us to digest starchy plant foods, foods with many of the dietary properties of the potato or the yam. It is likely that our early tool use and moderate brain size allowed us to learn and culturally transmit the cultural practices required to sustain this early "cooking" niche.

As our tool use and our social cooperation became more proficient, around a million years ago we added frequent hunting to our ecology, which led to another change in our diet and activity levels. This was when our brain sizes started to expand rapidly, thanks to genetic evolution. It is also when we are thought to have acquired an improved capacity to digest and transport fats within our bodies, particularly compared to other ape species, which eat prey much less often.

But notice the time-scales of these transitions. We spent several million years adapting to a diet that featured digging, gathering, and cooking roots and tubers. We then spent about a million years adding hunting to our underlying gathering/cooking way of life, and evolving accordingly. By contrast, even the agricultural populations of greatest age have been using grass seeds as their predominant nutrient only for tens

of thousands of years. This set the stage for a remarkable evolutionary transition, but one that is still “in process,” rather than a settled achievement of evolution. This is the key point for a possible revolution in human health, a revolution to which we now turn in the 55.

47. This novel agricultural lifestyle initially depressed adaptation and health, leading to intense natural selection for adaptations to the digestion of foods derived from grasses and milk, which has since produced adaptation to agricultural conditions at early ages.

There are a variety of ways to understand what has happened to agricultural populations over the last tens of thousands of years. I will focus on two.

Paleoanthropology supplies us with a long historical sequence of human skeletons to study. Before the advent of agriculture, our preserved skeletons show that we grew to a fair height, men averaging about 5 feet 5 inches to 5 feet 10 inches, women perhaps four or five inches shorter than this, on average. Close inspection of such skeletons indicates fair nutrition, although orthopedic injury was common.

With the advent of agriculture, the skeletons suggest an abrupt reduction in average height. This is also sometimes associated with evidence of chronic disease and poor nutrition. In Egyptian mummies, for example, there is evidence of chronic cardiovascular disease.

But all that evidence is indirect, and at least somewhat arguable. Fortunately, we have still better evidence of the kind assembled by Lindeberg in his "Food and Western Disease," already mentioned. For we have clinical medical data on the effects of adopting Western foods and lifestyles on twentieth century relics of hunter-gatherer populations. And those clinical data are damning: switching from a hunter-gatherer lifestyle to an agricultural and sedentary one produces a wide spectrum of chronic pathophysiologies, especially the early and devastating onset of age-associated chronic diseases.

The first conclusion to be derived from these findings is that the original switch to agriculture must have produced significant biological challenges, impinging on both functional capacity and the kinds of robustness that would affect sexual selection. Thus, natural selection would not have been relaxed by the advent of agriculture. Rather, it would have significantly changed direction.

The second conclusion to be derived is that over the hundreds of generations of selection for adaptation to agriculture, there must have been a wide array of genetic changes. Probably not many complete "selective sweeps," in the language of population genetics, but certainly many gene frequency changes across the genome, from what we now know of the genomics of experimental evolution. Furthermore, among long-agricultural human populations, these extensive evolutionary genetic changes probably provided us with extensive re-tuning of our functional adaptations, enabling us to thrive as young people growing up with foods derived from seeds and

milk, despite the daily back-breaking labor required to cultivate, harvest, and process the plants and animals which give us these dietary staples.

Thus modern humans with predominantly agricultural ancestry are not like cats who will sicken on cereal diets. Nor are we like those with strictly hunter-gatherer ancestry, who show much more acute onset of chronic diseases on Western diets. Thus much of the "paleo-diet" literature is overdrawn and invalid, for most of the present-day populations of our species.

48. Agricultural populations have also undergone substantial increases in population size compared to those of their ancestral hunter-gatherer populations, which increased the effectiveness of natural selection at later adult ages, resulting in the evolution of a delay in the cessation of aging under agricultural conditions.

In addition to the massive change in natural selection arising from altered diet and activity, agricultural civilizations feature radically increased effective population sizes, especially since the advent of recorded history. If this concept is elusive to you, think about the following question: how many people of the opposite sex could you have met, copulated with, and had children with during the last twenty years? I don't mean what multiple of individuals, I mean even if it were just one person, how many people on the planet, conceivably, could you have mated with?

The answer is around one or two billion, allowing for the too young and the too old. This is because we have had access to efficient air travel over the last twenty years, and for much of this period travel has been relatively unrestricted, leaving aside police-states like North Korea, Cuba, and Iran. That, crudely, is the scale of effective population size of our species at present.

During the hunter-gatherer phase of our evolutionary history, the total number of individuals available for mating to any one individual was orders of magnitudes less. Travel was not very efficient, as we had neither horses nor roads. And our population densities were vastly less. Perhaps you would have had a "dating pool" of some thousands.

In agricultural civilizations, such as those of ancient Rome or China throughout the last two millennia, there were good roads and wide circulation of merchants, soldiers, and slaves within and just beyond the perimeters of such societies. There were hundreds of thousands of individuals with whom a person might conceive children in their lifetime. Marriage would have been socially or legally constrained by conventions of nationality, class, or caste. But a significant amount of fertilization would have involved slaves, prostitutes, concubines, mistresses, rape, and other "less official" forms of mating, enough to ensure a very large effective population size.

The issue here is closely related to the premises with which the 55 began. Natural selection works with full effectiveness only in large populations, and at early ages. Species with population sizes like those of hunter-gatherer humans had the effectiveness of natural selection greatly constrained by population size, because we were not a particularly abundant species compared to those of most insects, or even those of many small mammals. Large mammals have some of the smaller population sizes among all animal species. It was only with the advent of agricultural civilization

that human populations became large, and these populations have furthermore been much more integrated in terms of opportunities for mating.

49. In agricultural populations over the last ten thousand years, the longer-sustained effectiveness of natural selection has resulted in an age-dependent pattern of falling adaptation to agricultural conditions in which functional decline is sustained over a longer period than was the case under hunter-gatherer conditions.

Thus the reach of natural selection has been extended deeper into adulthood among the agricultural populations of the last tens of thousands years. As a result, at least under agricultural conditions, individuals with agricultural ancestry should have an aging period that lasts significantly longer than that of individuals without agricultural ancestry, at least when they follow their ancestral lifestyles.

Indeed, considering human demography compared to that of well-studied model organisms like fruit flies, we have an extremely protracted aging phase. Few people survive long enough to reach the demographic phase in which "aging stop," as shown in some detail in our 2011 book, "Does Aging Stop? (Mueller, Rauser, and Rose; Oxford University Press). This, we believe, is the reason why gerontologists have long thought that aging is an unremitting process of physiological deterioration, because humans have been taken as the generic case of aging.

By contrast, hunter-gatherer populations should have an underlying pattern of aging more like that of the fruit flies that we have studied in our laboratories at UC Irvine. That is, they should show a relatively short period of aging that takes them to mortality and fertility plateaus on which much function is relatively long-sustained, at least if we contrive the analog of laboratory conditions for such populations. This would mean the provision of excellent conditions, with no shortages of food, protection from predators or criminals, and a relative absence of acute infection.

Now, hunter-gatherer populations do not in fact live this way. In some cases, they continue with a hardscrabble existence on the margins of the best habitats for agriculture, fighting tribal wars, and engaging in a pattern of competitive homicide that kills them off at a fair clip. The indigenous populations of the Amazonian jungle used to follow this pattern fairly extensively. And they also face death due to predators, including large felids and poisonous snakes. Accidental or violent injury readily leads to rapid death due to sepsis or hemorrhage among such populations, if there is no access to emergency medical services.

Or these populations are "semi-civilized," consume milk and seed-derived foods, and receive more access to medical care. But then they suffer the chronic health problems which their lack of adaptation to agricultural foods and inactivity will engender. Many of the people on "reservations" live this way.

Thus we have not been able to observe large human cohorts with early cessation of aging, because those individuals who have the genomes to exhibit this pattern do not live in a manner in which it could be exhibited. Those of us who do have such environmental conditions, in the general sense of good medical care and lower levels of violent death, do not have evolutionary histories in which our aging phase was curtailed at early ages.

50. Children and young adults with predominantly agricultural ancestry are well adapted to agricultural conditions of nutrition and activity, but children and young adults without agricultural ancestry are not adapted to such conditions.

Let us address with particular care the diet and the activity patterns of children, with respect to the relationship between such lifestyle questions, their health, and their evolutionary ancestry.

It is a straightforward corollary of the points that we have outlined to this point that children weaned from human breast milk should be fed and cared for in ways that depend on their ancestry. Those children whose ancestors were never subjected to agricultural conditions should not be fed novel agricultural foods, including but not necessarily limited to flour derived from grass seed and the milk of cows and other ungulates. There are probably other agricultural foods that they may be adapted to, such as many fruits, nuts, and a variety of "salad" vegetables, including lettuces and the like. Potatoes, yams, carrots, and other plant storage organs may also be harmless foods, particularly if cleaned and cooked so as to destroy any toxic compounds used by such storage organs to fend off nematodes, fungi, and other organisms that would otherwise consume the nutrients in such structures. However, there is still a significant amount of anthropological research that is needed to determine which dietary components can be safely consumed by children who come from populations that have never adapted to agricultural conditions. A further point is that such children probably have fewer adaptations to recurrent viral infections, due to the lower incidence of viral pandemics among hunter-gatherer populations. Thus they may not fare as well in large schools, due to recurrent infection.

Children with predominantly agricultural ancestry have been rigorously selected for dietary and other adaptations to agricultural conditions, including a higher level of exposure to viral infections. These children can eat pre-industrial agricultural foods, such as bread, rice, or cow milk, to the extent that their evolutionary ancestors consumed such diets. These children will also fare better in large schools, and under urbanized conditions generally, due to greater resistance to contagious diseases.

The term "children" here would refer to individuals who are at ages during which the forces of natural selection remain quite high, which would certainly continue into the early twenties, with respect to years of age. But in this sense, individuals over the age of thirty years are no longer children who have benefited fully from antecedent natural selection over hundreds of generations.

A further issue that arises is how to treat children with mixed ancestry, in terms of the proportion of their ancestors who have been subjected to selection for adaptation to agricultural conditions. In such cases, it is probably better to err on the side of

treating such children more in the fashion appropriate to those from non-agricultural lineages. They may retain some reasonable level of adaptation to non-agricultural diets and lifestyles, together with an admixture of attributes that will enable them to endure some features of the agricultural lifestyle. Finally, it should be noted that those whose ancestry is from the margins of agricultural civilizations, like the northern Scottish or the Mongolian nomads, may have significantly less adaptation to agricultural conditions than those from the long-established centers of such civilizations, such as Egyptians or Han Chinese.

51. Older adults from all human populations are not adequately adapted to agricultural patterns of nutrition and activity, resulting in an amplification of aging under such conditions.

Naturally, older adults from non-agricultural populations will be no better adapted to agricultural conditions than their children. Indeed, they will probably fare worse to the extent that agricultural foods are nutritionally similar to human milk, which almost all humans are able to digest well from birth.

It is when we turn to older adults with agricultural ancestry that the evolutionary analysis becomes interesting. I have argued to this point that the hundreds of generations of selection that some agricultural civilizations have imposed for that pattern of nutrition and activity will have extensively, albeit not necessarily completely, adapted children from such populations to these conditions. But such extensive adaptation applies only to the ages during which the forces of natural selection are near their maximal values.

At later adult ages, the forces of natural selection progressively fall. At these ages, there will have been less age-specific selection for adaptation to agricultural conditions, even in populations that have been subjected to such conditions for hundreds of generations. Thus, to the extent to which there is age-specificity to such selection, older adults will suffer from attenuated adaptation to the evolutionarily novel conditions of agricultural life. Such older adults will benefit from whatever age-independent adaptations to agriculture have been built by natural selection. But the very high mortality levels of post-aging humans from agricultural populations consuming agricultural diets, between 40 and 50 % per year, suggest such age-independent adaptation has been relatively limited.

In effect, older humans from agricultural lineages revert to a condition of poor adaptation to agricultural conditions which could be comparable to that of individuals with hunter-gatherer ancestry. But it is possible that they may retain some residual adaptation to hunter-gatherer conditions, if such adaptation has not been entirely corroded by selection acting at earlier ages. Given that many humans also vary in the extent to which their ancestry is agricultural, each older adult will have a specific mix of retained or compromised adaptation to hunter-gatherer diets and activity patterns. But what we can fairly sure of is that they will no longer have much adaptation to novel agricultural conditions; there has been too little evolutionary time for the later reaches of the human life-history to be fully remolded. This applies even among populations which have children that fare quite well under agricultural conditions.

This provides the possibility of enhancing the level of adaptation among older adults from agricultural lineages by switching them from agricultural diets and activity levels to those of hunter-gatherers at later adult ages. However, the extent of any such

enhancement will vary among these individuals. Practically speaking, it is an empirical question with an answer specific to each person.

52. All people without significant agricultural ancestry should revert to patterns of nutrition and activity which have physiological effects like those of hunter-gatherer lifestyles, in order to slow their aging and hasten its cessation.

The case of individuals who do not come from long-established agricultural populations is much less ambiguous. All such individuals should avoid (i) agricultural foods, (ii) exposure to the abundant pathogens harbored by agricultural societies, and (iii) activity patterns more appropriate to the cultivation of crops or the herding of dairy animals. Individuals with such ancestry who avail themselves of modern medicine, sanitation, vaccination, and the like, but avoid the forgoing environmental factors, could have their medical prospects can be transformed.

As Lindeberg documents extensively in his book "Food and Western Disease," such individuals can obtain dramatic relief from chronic Western diseases by avoiding the diet and activity patterns of the Western lifestyle. His data show a dramatic improvement with respect to the risks and debilitation of specific chronic medical conditions, such as diabetes, among those who have done this.

In Hamiltonian terms, what occurs with such lifestyle transitions, among individuals with non-agricultural ancestry, is a recovery of high levels of adaptation, or Darwinian fitness, upon reversion to the physiological environment to which these populations are well-adapted. If the tools of modern medicine and public health are added to such a recovery of adaptation, these populations will have transformed their aging process. They will have a higher level of adaptation when young, and will not be subjected to as rapid a deterioration when older.

But there are still greater possible benefits. For the demography of life-history evolution in such hunter-gatherer populations is very likely to have entailed the potential for a much earlier age at which aging stops. Among these populations, if they make the lifestyle transition that I am recommending here, it may be possible for them to halt their aging at a surprisingly high level of function, and then sustain that high level of function indefinitely. These individuals, in effect, have the potential to be the vanguard of post-aging human life. Given sufficient attention to their intermittent medical needs, they may show the rest of the species what the eventual "defeat of aging" might look like for the rest of the species.

It should be born in mind that this prospect is available only to those whose ancestry has suffered the least introgression of gene sequences from agricultural populations. There are no doubt relatively few people like this alive today. Yet they are among the most important test-cases for the conquest of aging in our time. As such, it would behoove the rest of us to treat them particularly well, as research with them may offer

us some of our best clues as to how we can escape from our protracted and severely debilitating aging.

53. Young people with significant agricultural ancestry can sustain their health with agricultural patterns of nutrition and activity, but not with an evolutionarily novel industrial lifestyle.

It is tempting to suppose that young people with agricultural ancestry are so well-adapted to novel foods that they can do well regardless of what we feed them, or how little exercise they receive. It may well be true that their high levels of function will probably enable them to cope to some extent with the pathological novelties of many of the foods that are advertised on television, particularly compared to older adults.

But it is virtually certain that such children would fare better with an "organic" agricultural diet free of refined sugars, trans-fats, high-fructose corn syrup, and the long list of chemical additives that are put into processed foods. And the same strictures would apply with even greater force to toxic residues of pesticides, the industrial chemicals that are used to coat cans and plastic bottles, and so on. To the extent to which an industrial compound has any biological activity, it constitutes a novel environmental factor to which no one is now adapted.

Refined sugars alone illustrate this point perfectly. Modern-day dental treatment of young people is necessary primarily because of the exposure of their teeth to high levels of dietary refined sugar. Among hunter-gatherer populations who do not consume Western foods, the cavities and other forms of oral decay that are so common in young people living in industrial societies, by contrast, are almost wholly absent. Even those who adopt a more "organic" agricultural diet are spared much of this dental deterioration. And later in life, massive sugar exposure fosters the onset of type II diabetes.

This is not an argument against novel environmental factors that have direct and unequivocal health benefits. Those who face acute viral, bacterial, fungal, protozoan, or helminth infections are well-advised to take the corresponding antiviral, antibiotic, antifungal, and anti-parasite chemical agents. These all can and do save lives. Nor is this an argument against vaccination, pasteurization, personal hygiene, or the sterilization of medical equipment. Well-researched and screened pharmaceuticals or medical procedures can afford great benefits to all of us.

It is also virtually certain that young people, like the rest of us, are not suited to the modern-day pattern of restricted physical activity, with long hours of enforced physical passivity as well as the addictive pursuit of athletically inert activities, like video-gaming or using social media. It is in the practical interest of many industrial institutions to keep all of us, and especially the young, as inert as possible. But such inactivity is directly inimical to our health at ages much above three years. The volume of medical and epidemiological data illustrating this evolutionarily basic point is vast, and hardly needs to be labored over here.

54. Older adults with significant agricultural ancestry cannot sustain their health with either agricultural or industrial patterns of nutrition and activity, and should instead switch to hunter-gatherer patterns of nutrition and activity in order to slow their later aging and possibly hasten its cessation.

No one who has any alternative should sustain an industrial diet of heavily processed, highly sweetened, pre-packaged foods. Acute starvation or the consumption of pathogen-ridden foods would be worse, but even if overall calorie intake is somewhat reduced, we would be better off forswearing such diets. Indeed, industrial foods are probably better regarded as early-stage substances of abuse, substances that induce cycles of dependence, addiction, and binging that prepare young consumers for later careers abusing alcohol, nicotine, caffeine, and other drugs of addiction or abuse. Industrial patterns of consumption abuse our bodies, and set our brains up to sustain patterns of compulsive and extreme use of still more dangerous substances. Of particular note is the point that, as industrial "foods" chronically inflame our tissues, they foster degenerative processes that will eventually make us dependent on painkillers that will lessen the chronic pain and suffering that these substances engender. Thus industrial foods foster the profits of pharmaceutical companies.

There is really only group that one can recommend an organic agricultural diet to, the young people with ancestry solely from long-established agricultural populations. It is even possible that they will fare better on this diet than they would on a hunter-gatherer diet, although one cannot be certain of this.

For EVERYONE else, the agricultural diet and lifestyle should be considered a potential health risk. I have already discussed the remarkable opportunities that may be available to those who have little agricultural ancestry, if they revert to their recently ancestral lifestyle. At this point, I would like to propose further that all older adults consider trying elements of the hunter-gatherer lifestyle, with respect to both nutrition and activity. For most of us, it is quite likely that our aging phase will be greatly ameliorated. I would expect many to enjoy a reduced level of risk of cardiovascular disease, cancer, and metabolic disorders, like type II diabetes. This does NOT mean that I expect such chronic disorders to be cured, once they have arisen, or to be entirely prevented. My view is that every adult is at some risk of dying from these chronic disorders, including those on mortality plateaus after the cessation of aging. The prospect instead is that the rate at which such chronic disorders arise, and their severity, should fall among many of those older people who stop living in a manner which elicits the physiological effects of an agricultural way of life, or the still-worse effects of an industrial way of life.

An interesting and important question is whether those with agricultural ancestry who make a later-life "paleo-switch" will also enjoy an earlier cessation of their aging. This

is a research question that my laboratory is actively working on at the moment. Early results suggest that there may be an earlier cessation of aging upon such switching, but we are still working on it.

We also do not know if there is a critical age past which making such a switch has no beneficial effect. That is also a research question, one that we have yet to address. We hope to do so soon.

55. Once this switch to a hunter-gatherer lifestyle among older adults has become widespread, further changes that would enhance human health at later ages can be discovered using evolutionary research tools, such as experimental evolution with model organisms and the molecular genetic analysis of human evolutionary history.

In the previous ten theses, I have presented the scientific case for a particular type of dietary and lifestyle intervention that, I contend, should give some health benefits to a large number of middle-aged and possibly older adults. In the case of those with hunter-gatherer ancestry, the benefits from this switch could be spectacular.

But even so, this is only the start of a revolution in human health that I expect to occur during this century. The cold grey grip of the reductionist biomedical establishment will be progressively weakened by the onslaught of reductionism-killing genomic data. That establishment is like the Aristotelian natural philosophers who were mainstays of the Catholic establishment during the Renaissance, full of power, prestige, and support. But dead wrong, even as they received funding for their indulgences. As the Procrustean dogmas of twentieth century cell biology are killed off, we will be able to transform human health using tools afforded to us by the burgeoning new biology, a biology that is better equipped to handle the exponentially-growing onslaught of "omic" data, whether genomic, proteomic, transcriptomic, metabolomic, or other-omic. This new biology will be founded on formal theoretical tools, especially an upgraded evolutionary genetic theory that has been refined and strengthened by access to the genome-wide data that it has long needed.

With the new genomic biology, we will discover how our metabolisms need to be re-tuned in order to slow our aging and even end it earlier. With further advances in stem-cell technology and nanotechnology, we will become steadily better at replacing cells and repairing tissue matrices that have become worn or acutely damaged. Larger-scale structures, like livers or spleens, will be re-built from our own stem cells, so that they can be replaced without long-sustained immune suppression.

Over time, the chronic diseases that make our later lives so miserable will become as controlled and limited as contagious disease is in our time. Many still die of infections, but contemporary medicine now has the tools to rescue most of those with infections whom it can attend to in a timely fashion, providing it is given adequate resources. By the end of this century, the same will be true of most of our chronic disorders, like those of the cardiovascular system. In the year 2100, death from aging-associated disease will seem as unusual as death due to infection now is in affluent industrialized countries. It will still happen, but it will not terrorize us as it does now.

But achieving this salubrious outcome will require that the presently entrenched forces of the biomedical establishment be overthrown. Overthrown not by the naïve or the

self-deluding, but by those who see clearly the scientific failure of the twentieth century biomedical reductionism which fuels the prestige and the profits of the medical-pharmaceutical industrial complex. Fortunately, this revolution does not need to be fed first by the blood of protesters, but by the simple act of thinking twice before reaching for the brightly colored packages on supermarket shelves.

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