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REVIEW ARTICLE

Four steps toward the control of aging: following the example of infectious disease

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Abstract The biotechnological task of controlling human aging will evidently be complex, given the failure of all simple strategies for accomplishing this task to date. In view of this complexity, a multi-step approach will be necessary. One precedent for a multi-step biotechnological success is the burgeoning control of human infectious diseases from 1840 to 2000. Here we break down progress toward the control of infectious disease into four key steps, each of which have analogs for the control of aging. (1) Agreement about the fundamental nature of the medical problem. (2) Public health measures to mitigate some of the factors that exacerbate the medical problem. (3) Early biotechnological interventions that ward off the more tractable disease etiologies. (4) Deep understanding of the underlying biology of the diseases involved, leading in turn to comprehensive control of the medical problems that they pose. Achievement of all four of these steps has allowed most people who live in Western countries to live largely free of imminent death due to infectious disease. Accomplishing the equivalent feat for aging over this century should lead to a similar outcome for aging-associated disease. Neither infection nor aging will ever be entirely abolished, but they can both be rendered minor causes of death and disability.

Keywords Aging · Medicine · Evolution · Human health

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Introduction

If human aging were a simple biotechnological problem, we would have solved it by now. After all, there are few human problems of more sustained interest than the control of aging (Gruman 1966). The history of this endeavor is as old as written records of human civilization, from the legend of Gilgamesh's vain quest for immortality to Ponce de Leon to the present-day life extension movement (Haycock 2009).

The first author of this article has been entangled in attempts to address the problem of human aging for more than thirty years (e.g. Rose 1984a, 2005), and is still perennially encouraged to address it at symposia, in journal articles, and in books. The present article arose from a talk given at a recent meeting devoted to the prospects for defeating aging in the twenty first century. After decades of reflection on this problem within our laboratory group, we believe that we now have a relatively clear road-map to offer, one based in part on our scientific work over the last four decades.

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Our proposed strategy is based on the precedent of the control of infectious disease. Before the nineteenth century, infectious disease ravaged human populations largely unchecked. Plagues would arise and spread, sometimes reducing human numbers to barely half of what they had been just a few years before (McNeill 1976). Yet starting in the middle of the nineteenth century, Western science and medicine embarked on a long campaign that led to the effective control of infectious disease by the end of the twentieth century. For example, between 1900 and 1996 infectious disease mortality in the United States declined over 90 % (Armstrong et al. 1999).

Here we use this historical precedent to frame a strategy to control aging by the end of this century. In particular, we break down the human conquest of infectious disease into four key steps. These same four steps are necessary for the conquest of aging as well, we will argue.

Step one: agreement about the nature of the problem

We have lived for so long with effective control of infectious disease, it is hard for us to understand that the causes of infectious disease were obscure in recent historical times. It took determined research and advocacy by both Louis Pasteur (1822–1895) and Robert Koch (1843–1910), among others, to establish the germ theory of disease. Knowledge of microscopic organisms dates back to the time of Antonie van Leeuwenhoek (1632–1723), and was growing rapidly in the nineteenth century. Nonetheless, many nineteenth century biologists believed in spontaneous generation of life from inanimate materials like dirt and water. Like most physicians throughout premodern history, European physicians of the nineteenth century generally believed in "miasma" theories of infection, which blamed "bad air" for epidemics of disease, rather than any living agent.

The war against the miasma theory was one of long duration, but key turning points can be identified. In 1840, Jakob Henle—one of the nineteenth century's founders of scientific medicine—cogently formulated the germ theory of infectious disease that had been clinging to life in the shadows of the dominant miasma theory of disease. In the 1850s, John Snow traced a cholera epidemic to a water pump in London. A long series of experiments carried out by Louis Pasteur and his colleagues starting around 1860 were key to establishing the germ theory of infectious disease. These experiments demolished the miasma theory of disease and validated the use of vaccination to prevent specific viral diseases. In 1876, Robert Koch published experiments which unequivocally demonstrated that the disease anthrax was caused specifically by the bacterium *Bacillus anthracis*. By 1890, controversy about the causes of infectious disease was essentially over. Microbiologists and physicians en masse began the long and arduous medical campaign against infectious disease without further arguments about the fundamental causes of infectious disease.

We are now in a similar situation with respect to the fundamental causes of aging. There are two broad schools of thought on aging. The now predominant idea, like the miasma theory before 1860, is that aging is caused by cumulative damage and/or progressive physiological disharmony. This theory has taken on different guises since it was first proposed by Aristotle more than 2300 years ago. But all versions of this theory assume that aging is a physiological process that cumulatively undermines health. In the hands of current scientific polemicists, like Aubrey de Grey (e.g. de Grey and Rae 2007), aging is explained by analogy with the breakdown of a car or house that does not receive adequate maintenance. With this assumption, the key physiological mechanisms of damage and disintegration that underlie aging are to be identified and stopped.

Opposed to this view is the evolutionary theory of aging (e.g. Hamilton 1966; Charlesworth 1980; Rose 1991), which is based on the mathematical result that the forces of natural selection fall with adult age. Falling natural selection then leads to a pervasive loss of adaptation and thus declining physiological functions. This evolutionary theory of aging is specifically *not* a theory based on some physiological process of deterioration (vid. Rose et al. 2012).

If the evolutionary theory of aging is incorrect, then it should have failed to pass the many strong-inference tests that it has endured since 1980 (vid. Rose 1991; Mueller et al. 2011). But it has not failed any of these tests.

If the physiological theories of aging are correct, then the following well-established results should *not* have been found. A variety of fissile invertebrate species do not exhibit aging. Aging readily evolves in

laboratory populations when the forces of natural selection are changed. Aging comes to a stop in some experimental cohorts at later ages after their forces of natural selection have stopped declining. Yet all of these results have been found.

It took about 40 years for the evolutionary genetic basis of aging to be formally developed (e.g. Haldane 1941; Hamilton 1966; Charlesworth 1980). After that, it took another 30 years to extensively test this theory experimentally (e.g. Rose and Charlesworth 1980; Luckinbill et al. 1984; Rose 1984b; Rose et al. 2004; Mueller et al. 2011). Among the advantages of the evolutionary theory of aging are the following. (a) It is derived mathematically from assumptions that are not in dispute (vid. Charlesworth 1980). (b) It can account for the phylogenetic diversity of the physiology of aging (Rose 1991). (c) It explains why some species do not age (Bell 1984; Martinez 1998). (d) It can explain why aging stops sometimes late in life (Mueller et al. 2011).

Our *scientific* conclusion is that aging is best explained by the evolutionary theory developed for it, particularly since 1966, and extensively tested, particularly since 1980. There is no physiological necessity to aging, and aging is not caused by a cumulative, unitary or multifold, physiological process.

Most evolutionary biologists are convinced that merely physiological theories of aging are incorrect. Why do these false ideas persist? Four barriers prevent the general acceptance of the evolutionary theory of aging. First, the evolutionary theory of aging relies on mathematics that are beyond the ability of most cell and molecular biologists. Second, invertebrates that do not age at all are of little interest to biologists who study aging in mammalian species, among which aging is universal. Even biologists who study aging in invertebrate species chosen because they exhibit rapid aging have little interest in studying species like those fissile coelenterates and fissile worms that do not age at all. Third, the data from experimental evolution which directly support the evolutionary theory of aging are of negligible interest to cell and molecular biologists who have little knowledge of present-day evolutionary research generally. Fourth and finally, the institutional edifices of aging research, from the National Institute of Aging of the United States to virtually all of the private foundations that support aging research at this time, are entirely founded on cell-molecular theories of aging which accept the dominant premise that aging is a physiological process. Much the same was true of the miasma theory in the 1850s and 1860s, when it was upheld by both leading medical practitioners and governmental agencies.

If the vast majority of research on aging interventions is predicated on fundamentally erroneous theories about its causes and nature, then little progress will be made toward its effective control. Our *practical* conclusion is that biologists must abandon the theory that aging is due to cumulative physiological processes. This is a necessary first step toward the eventual control of human aging. Until that step is taken, controlling the biomedical problem of human aging will depend almost entirely on those few scientists who both accept the evolutionary theory of aging and work on the problem of aging interventions.

Likewise, progress with the problem of infectious disease was confined to relatively few scientists and physicians from 1850 to 1890. It was only after the scientific victory of the germ theory of disease was widely appreciated that the public health and medical communities could proceed with a large-scale assault on the problem of infectious disease.

See Fig. 1 for an historical timeline for the control of infectious disease.

Interactions between loss of adaptation, chronic infection, damage, and cancer

Age-dependent decline of adaptation is not, however, the only pathophysiological process that impinges on human health. Evidently the progression of untreated, or worse still untreatable, chronic infectious diseases can also produce progressively worsening pathophysiology. Before 1940, syphilis was an example of such a disorder. HIV had similar effects before the advent of contemporary antiviral treatment regimes. To the extent to which patients suffer from unresolved chronic infection, such infections will complicate interventions that focus solely on aging as we view it.

In the same vein, exogenous damage at every level can have a cumulative adverse impact. An extreme example would be a viral infection that leads to damage to a particular organ or structure, from the pancreas to a heart valve. Such events will exacerbate and complicate the human loss of adaptation with adult age. Similarly, damage to a limb or the spinal column can have multiple clinical consequences that will impair physiology in an age-dependent manner;

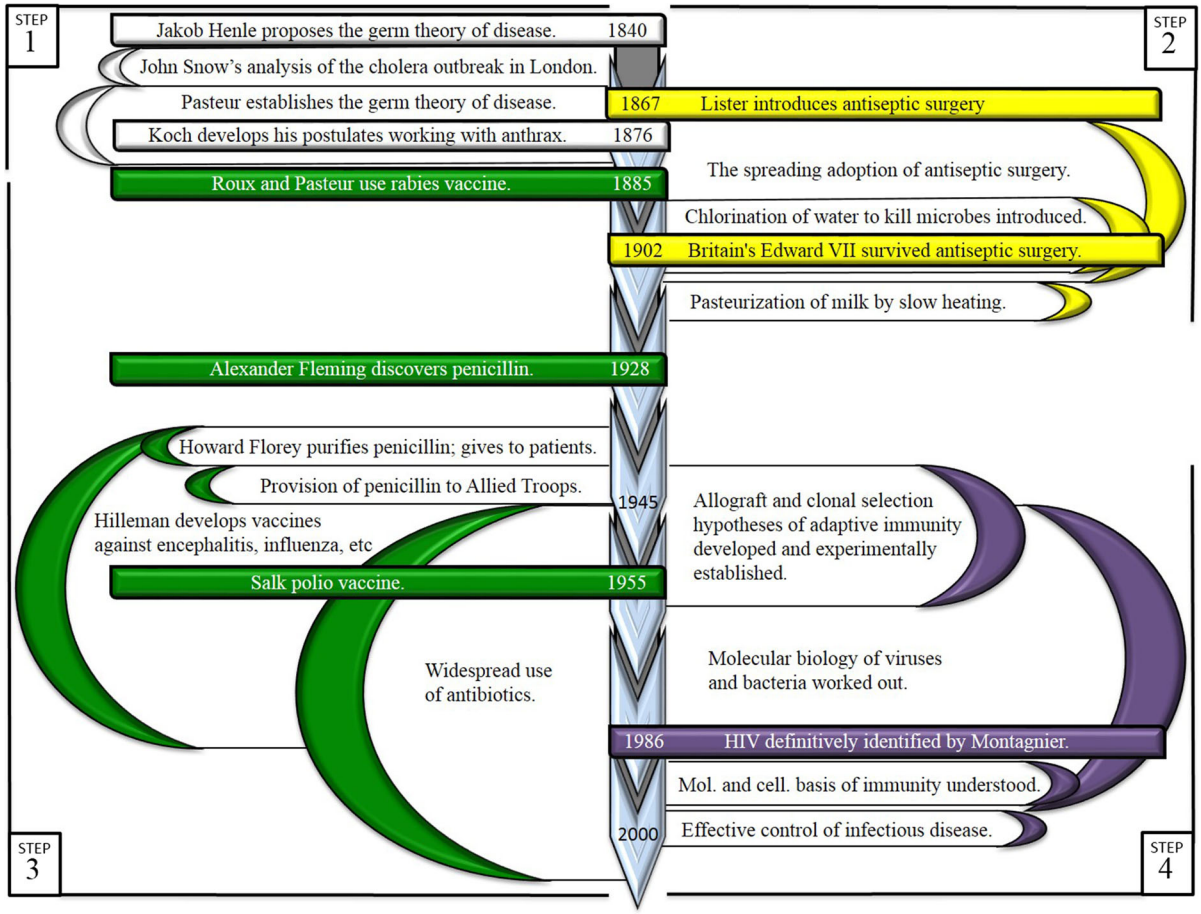

Fig. 1 Timeline for the control of infectious disease

for example, a disabling injury can reduce patient activity and thus create problems for maintenance of both cardiovascular and neurological function, in part by increasing the risk of diabesity.

Somatic mutations that give rise to cancer is an example of a physiological process that can interact with loss of adaptation to pose mortal threats to our survival. Evidently, oncogenic processes can give rise to cancer in children and are not specific to aging, but they also have a strikingly age-dependent increase in risk among adults. This is a frighteningly perfect instance of the ways in which the loss of adaptation with age that is expected from the Hamiltonian theory of aging can interact with the kind of cumulative physiological processes that are the hallmark of the Aristotelian tradition for explaining aging.

The miasmatists were right about the need to make our water supplies and food smell better, even though they did not accept the microbiology behind that need. Likewise, much medical work on the problems of (i) cumulative exogenous damage to our bodies, (ii) oncogenesis, and (iii) chronic infection has practical value for the treatment of age-related chronic diseases. Such medical interventions are important for chronic health, even though such work is not addressing the underlying phenomenon of aging, which will occur even in pathogen-free environments among animals that have their incidental damage fully repaired.

Step two: public health measures to mitigate disease

There are immediately practicable interventions that will partially alleviate human aging, interventions that derive from evolutionary reasoning. We have only

recently come to this view. Previously, we had supposed that no measures based on the evolutionary theory of aging were available to intervene at a public health level. But we now believe that we were wrong about that.

Though authors of science fiction and journalists like to suppose that scientific breakthroughs will immediately lead to useful new inventions, the history of technology suggests otherwise. The development of evolutionary genetics from 1900 to 1930 did not immediately lead to great improvements in crop and livestock breeding. That took decades of further applied research, instruction at agricultural colleges, and large-scale corporate breeding programs.

Likewise, the acceptance of the germ theory of infectious disease led to decades of work on the following public health measures: provision of clean water; effective disposal of human wastes; hygienic mortuary practices; food inspection for microbial contamination; pasteurization of milk; and so on. These public health practices were responsible for the widespread elimination of much infectious disease as a cause of death.

Simple changes in medical practice complemented such public health programs: cleaning wounds before bandaging; antiseptic operating rooms; physicians washing their hands between patients; and so on. Once physicians clearly understood that many diseases are caused by pathogenic microbes, then simple counter-measures spread over the decades following the triumph of the germ theory of infectious disease.

Returning to aging, people can live longer and healthier lives, if they become more active and alter their diets. The fundamental reason for this is that our bodies are 'mismatched' with important aspects of modern industrialized life.

The evolution of aging depends on evolutionary history. Much of our present lifestyle is based on technologies and practices that are evolutionarily novel. Among these are powerful lighting at night, comfortable chairs, consuming large amounts of sugar, and motorized transport, all of which have become common only since the nineteenth century. Before the last few human generations, most people went to sleep not too long after sunset, walked a great deal, and had little processed sugar in their diets. We are now frequently exposed to entirely novel nutrients, preservatives, and emollients that have been introduced by the chemical industry. Substances like artificial sweeteners produce evolutionarily unprecedented combinations of sensation, nutrition, and satiety. All told, industrial civilization has given us diets and lifestyles of radical evolutionary novelty.

Some features of industrial civilization have improved our lifelong course of disease. Providing clean water and uncontaminated food to most people is a singular achievement of industrial civilization. Likewise, antiseptic surgery, antibiotics, and medical imaging have greatly improved the impact of medical care on our survival. Reverting to genuinely "natural" or "organic" lifestyles would shorten human life expectancies. We have no desire to undo Pasteur's microbial revolution in the practice of medicine.

But other features of industrial civilization have probably aggravated human diseases. The progression to type 2 diabetes has accelerated due to widespread consumption of soft drinks, candy, and pulp-free fruit juice, all of which lead to rapid spikes in serum glucose. Trans fats are chemically modified vegetable oils that were unknown before the twentieth century, a food ingredient that has now been definitively shown to exacerbate cardiovascular disease (Teicholz 2014). Sedentary lifestyles also foster chronic disease (e.g. Bijnen et al. 1998). From an evolutionary standpoint, the obvious suggestion is to avoid these features of industrial civilization which foment chronic disease simply because we are not yet evolutionarily adapted to them at any age, in any respect.

Some of our proposed diet and lifestyle changes are based on the notion that humans are not adapted to some aspects of industrial civilization. An important question, therefore, is how long does it take to become well-adapted? The answer is that the speed of adaptation is a function of selective pressure. All things being equal, the greater the selective pressure, the faster the evolutionary change. But the forces of natural selection fall with adult age, reducing the speed of adaptation at later ages. Since the forces of natural selection fade with adult age, older people will be less adapted to agriculture and living in cities than younger people (Mueller et al. 2011, Chap. 11).

As evolutionary biologists we have seen rapid responses to strong selection in the lab, with 30-40 generations considered relatively rapid. Let us consider the example of sedentary life. Currently, both young and old people who walk more suffer less from chronic disease. We expect that young people will be well-adapted to a sedentary lifestyle within 30 or 40

generations. If we assume 20 years per human generation, and further assume no other relevant change, then we predict that young "couch potato" humans would be adapted to a fully sedentary life somewhere between 500 and 1000 years from now. For older humans, we predict that such adaptation would take much longer—perhaps many thousands of years. So the 'public health' message is simple. Individuals and institutions that want to sustain health ought to walk more. This conclusion is a natural corollary of the mere evolutionary novelty of the indolence that industrial civilization enables.

Dietary change is the second immediate change that can increase health and lifespan. We favor a specific version of a 'paleo' diet for older people. Because there is a lot of popular writing on paleo diets, we first address some of the popular misconceptions.

A common misconception among advocates of the paleo lifestyle and diet is that human evolution stopped long before the adoption of agriculture (e.g. Eaton and Konner 1985; Cordain 2002). Recent research on rates of evolution in both laboratory (e.g. Rose et al. 2004; Matos et al. 2002) and natural populations (e.g. Zuk 2013) shows that populations which are given new environments readily adapt to them within dozens of generations, at least at younger ages. This is much faster than the thousands of generations of evolution that advocates of the paleo diet assume it takes to adapt to new foods.

Just as young people will adapt to sedentary life more rapidly than older people, young people are expected to adapt to novel "industrial" foods, like soft drinks, relatively quickly. In addition, young people who have long-agricultural ancestry are probably already evolutionarily adapted to agricultural conditions; older people will be less adapted to agriculture. Accordingly, we advocate that all people switch from organic agricultural foods after the age of 30 or so. People without a long agricultural ancestry may benefit from switching earlier than 30 (vid. Rose et al. 2014).

For older adults, evolutionary theory suggests the consumption of foods that most humans consumed before the advent of agriculture. At the core of this diet is cooked flesh and organs, including that of arthropods and mollusks. A wide variety of less-processed vegetables and fruit of the type that humans have long consumed are included as well. Furthermore, and perhaps surprising to some, humans apparently long consumed cooked tubers and other plant storage organs, like potatoes and other root vegetables. Finally, humans have a long history of consuming alcohol from decaying fruit, so some alcohol is included. The two biggest categories of food to be avoided are dairy and grains. Grass species became a major part of the human diet only after agriculture. Grains are frequently low in protein and include compounds that inhibit human physiology. (For example, rice inhibits the absorption of heme.) Just as sustained consumption of grain is a relatively recent feature of human life, so is the consumption of milk during adulthood. Other agricultural foods are problematic too. Legumes have several deleterious effects. Their seeds are built with chemical defenses against being consumed. Thus seeds, and oils derived from seeds, are to be avoided. Finally, there are a number of compounds that only became common for human very recently, on an evolutionary time-scale. Among those to be avoided are high-fructose corn syrup and trans fats (Table 1).

In summary, our "public health" advice is twofold. First, become more active. Walking 3–5 miles per day will, on average, have a significant positive impact on human health. Second, consume an organic agricultural diet when young and then switch to the type of paleo diet outlined above when over 30. We have seen first-hand the benefits from these two changes. It is possible for older people to improve their health substantially in a relatively short period of time. Many of the benefits of switching to an active lifestyle and a later paleo diet can accrue in less than 2 years.

Making these changes is hard for both internal and external reasons. On the internal side, behavioral economics has documented the difficulty humans have in changing behavior. The techniques for making such fundamental change are beyond the scope of this article. We do note that some people do however succeed in making big changes, and the promise of a healthier and longer life is sufficient motivation for some.

Beyond the internal challenges of behavioral change, those who choose this path will have to navigate a world filled with foods that are essentially poisonous. Supermarkets and restaurants of industrial countries are full of foods that older people should not eat, as well as foods that no one should consume in large quantities. It takes significant effort to avoid foods that are either "industrial" or "agricultural" in

Table 1 Suggested food consumption based on evolutionary theory

Foods to consume at any adult age	Foods to avoid later in adult life
Meat; animal organs	Dairy products including milk and cheese
Fish	Foods derived from grass species (e.g., wheat, rice, barley)
Vegetables	Legumes
Fruit and honey	
Tubers including potatoes	
Alcohol (in small quantities)	

their impact on human health. Similarly, it is difficult for most people to get to their places of work without the use of some form of motorized transportation, making infrequent walking commonplace. Artificial lighting after sunset disrupts patterns of sleep. Urban planning and food production need to change to reduce the adverse impact of our lack of adaptation to the industrial way of life.

Finally, diet and lifestyle changes will *not* abolish aging. Though aging-associated disease is rare in hunter-gatherer populations (vid. Lindeberg 2010), it is not entirely absent. Instead, an evolutionarily age-appropriate diet, we predict, will reduce the risk of chronic disease and increase everyday function. See Fig. 2 for the projected timeline for the control of aging.

A person convinced of the germ theory of contagious disease in 1840 could avoid infection by washing their hands, boiling water, getting cowpox vaccination against smallpox, and insisting on sterilized surgical instruments. But the large-scale public health revolution that followed, once both officials and physicians accepted the germ theory, would have benefited them still more. Far fewer physicians, water suppliers, and food providers were sources of infectious pathogens in 1940 compared to 1840.

Would reforming our lives based on evolutionary insights save as many lives as the public health measures adopted in light of the germ theory of disease? We doubt it. But it could do enough to make universal retirement between 60 and 70 years of age unnecessary.

Step three: attacking specific diseases as technology advances

Beyond diet and lifestyle, what can we do? The answer is that over some decades we can make enormous strides in improving human aging. We focus on two aspects of this prospect for progress against aging.

Progress requires decades of sustained effort based on the correct theory

Some of the more spectacular advances achieved in the campaign against infectious disease were achieved from 1920 to 1960. Vaccination advanced disease by disease. Antibiotics were discovered in the 1920s and were then widely supplied starting in the 1930s, with the excellent antibiotic penicillin first used widely in the 1940s. Advances in antiseptic surgery made procedures like Caesarian section safe by the middle of the twentieth century, and Western perinatal mortality plummeted. While these advances did not have the same quantitative impact on death rates as the provision of clean water, effective sanitation, and inspected food, they continued progress toward control of infectious disease. By the 1960s, infectious disease had lost its status as the chief killer of people in advanced Western countries. Diseases like smallpox, syphilis, gonorrhea, tuberculosis, and measles were beaten back almost entirely. These results were achieved by doing a fraction of what medicine is now able to do against infectious disease, but that fraction made a disproportionate impact relative to the lack of medical progress against infection in the centuries of Western medical practice before Pasteur.

In this vein, how can evolutionary research help with heart disease, stroke, cancer and type 2 diabetes? The first, and most important, point is that evolutionary research refutes the notion that aging is a physiological process. Something that does not exist cannot be stopped in order to cure chronic disease.

We advocate a disease by disease approach at first

The key to largely eliminating deaths due to aging lies in deep understanding of the genotypic and physiologic basis of mortality and morbidity. At a high level, there are two approaches one could take. At one

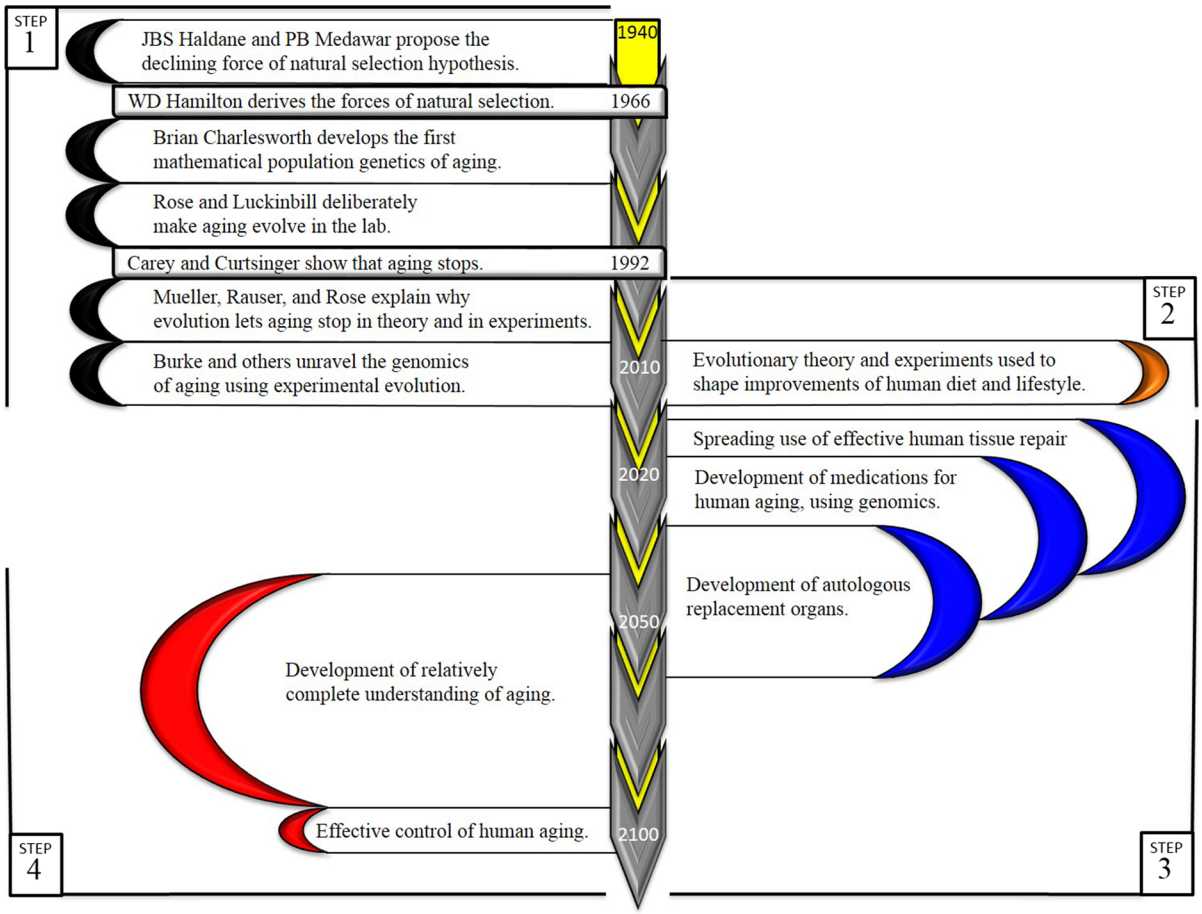

Fig. 2 Projected timeline for the control of aging

extreme, would be a focus on parsing the entire genomic machinery controlling human aging. The alternative that we favor is to continue some work on parsing the entire machinery of aging, but to put more effort for now into specific diseases that make up human aging, even with knowledge that remains incomplete.

Our motivation for favoring a disease-based approach is the vast complexity of the more general problem. All genes have roles defined by natural selection. Put another way, people have about 20,000 genes that contribute to adaptation, and thus our health. The evolutionary theory of aging is based simply on the de-tuning of our health with age due to weakening natural selection. Therefore, the complexity of the genomics of aging will approach the complexity of the entire genome. Our estimates of the number of genes involved in *Drosophila* aging are very large (Burke et al. 2010; Rose and Burke 2011; Phillips et al. in prep.). We expect that the genomic control of aging in humans is at least as complex as that of fruit flies.

This means that parsing the entire genomic machinery controlling human aging is extremely hard. We are still struggling with the genomics of human height, even though we have massive amounts of genomic data for height (Visscher 2008). For now, a better line of attack on human aging is to go after heart disease, stroke, cancer, and late-onset diabetes one at a time, just like the development of vaccines one infectious disease at a time.

Such a plan is reasonably parallel to how we made considerable progress with infectious disease in the first half of the twentieth century, before we worked out all of its molecular and cell biology. Instead of waiting for those scientific milestones to be achieved,

biomedical research plunged ahead with the development of antibiotics and vaccines, building incrementally on the progress that was begun in the early decades of the twentieth century. Though only a fraction of the molecular and cellular foundations of infection and immunity were figured out before 1960, great practical progress was made with that fraction. We propose that the same thing could be achieved with aging. From determining only a fraction of the mechanistic details of human aging, we might reduce the medical impact of aging to less than half of what it is now, perhaps even to less than a third of what it is now.

We have already pioneered this approach in our *Drosophila* research on aging. Early on, we discovered that increased lifespan in fruit flies requires increased stress resistance (Service et al. 1985). We followed up on that discovery by focusing on individual types of stress resistance, such as resistance to desiccation or starvation. We unpacked the physiological foundations of these two types of stress resistance, and found that they were quite different (Rose et al. 2004). Doing this was easier than resolving all the machinery of aging in *Drosophila*.

Similarly, focusing on individual, human, chronic diseases one at a time is likely to be more medically useful at the present time than taking on aging as a whole. For the next few decades, practical research on slowing the aging of specific human organs one at a time will be more useful for medical progress. Research on aging as a whole should still proceed, but it may yield medical pay-offs only later in this century. The analogy with progress on the problem of infectious disease between 1920 and 1960 is an important ground for understanding this. Much medical progress against infection was achieved long before biologists knew many of the important mechanistic details about infectious disease.

The addition of repair technologies to evolutionary technologies for controlling aging

During this transitional phase, say from 2020 to 2060, anti-aging medicine will not yet be grounded on a deep and comprehensive understanding of aging-associated chronic diseases. Heart, liver, and kidney disease will still arise and often damage such organs. Malignancies will need to be cut out of cancer patients. Thus there is every reason to welcome the use of organ and tissue repair technologies to the armamentarium of anti-aging research. Such technologies are developing quickly, in any case.

But there is an important distinction to be drawn. We are now in a position to develop medical treatments that involve macroscopic repair, yet we are far from having the capacity to repair most damage at a molecular level. That is the inspiring vision of Aubrey de Grey (e.g. de Grey and Rae 2007), but we suggest that achieving it is decades away. Long before then, organ-by-organ and tissue-by-tissue repair is our best prospect during the transition that we project to the late twentieth century deep mastery of aging.

Step four: exploiting deep and comprehensive understanding of diseases and defenses

As academics, we are attracted to the vision of a comprehensive understanding of the machinery of human aging. But given the scientific evidence of its complexity, we must be some decades away from such an understanding.

By 2000, biologists had assembled a comprehensive understanding of infectious disease. The complexities of adaptive immunity were well mapped. Innate immunity was distinguished from adaptive immunity, and its role as a first-line of defense against infection had been made clear. Genomes of viruses and bacteria were sequenced, and the molecular targets for vaccination, antiviral medication, and antibiotics were well known. Much of this scientific understanding *followed* rather than preceded the development of our most useful vaccines and medications.

But the value of this comprehensive scientific analysis fully proved its worth when the HIV epidemic surfaced in the 1980s. If we hadn't developed powerful scientific knowledge of infectious disease, HIV might have had an even more devastating impact on human populations. As it turned out, we were able first to identify and second to attack this deadly pathogen at great speed.

In the same vein, we predict that more progress will first be made with human aging by focused interventions, as outlined in Step Three. Indeed, such focused interventions may curtail the majority of deaths due to aging. But the last stages of the conquest of aging will require deeper and prolonged research on aging as a

whole that proceeds in parallel. For once chronic aging disorders like heart disease, cancer, and diabetes have been mostly brought under control, we will live long enough to face still later aging diseases. At least one of the reasons why Alzheimer's Disease is now increasing in incidence is that so many people now escape death due to infectious disease, cardiovascular disease, and cancer. Once cardiovascular disease and cancer are largely under control, chronic diseases like Alzheimer's that usually arise still later in our lives will become numerically predominant as aging-related causes of death and morbidity.

By that time, sometime later in the twentieth century, our hope is that we will have a comprehensive, powerful, and detailed understanding of aging, like we have now for infectious disease. Then aging will recede from our lives to the same extent as infectious disease has. People will still die of cardiovascular catastrophes, like the rupturing of aortic aneurysms, just as the unlucky still die of acute sepsis in our time. But death due to chronic disorders should be rare rather than common after 2100, unlike the way it is now. Instead, most people will die from accidents and misfortunes, whether automotive collisions or aggravated assault or warfare. By the twenty second century, average human lifespans could stretch well beyond two centuries, creating new complexities for politicians, civil servants, and actuaries to worry about.

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