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## Life history tradeoffs and the evolutionary biology of aging

### 5.1 Introduction

We commonly talk about our lives in terms of the life course or life cycle. Although each of us goes through a life cycle only once, there is a continuity of life cycles from generation to generation. Some biologists view life cycles as the fundamental units of biological organization and think about evolution as the evolution of life cycles (Bonner 1993; Sterelny and Griffiths 1999). Evolutionary life history theory provides a framework for understanding how natural selection has shaped life cycles in ways that optimize reproductive fitness (Charnov 1993; Stearns 1992). Life history theory provides a coherent view of the entire human life cycle and is especially important for medicine because it underlies the evolutionary theory of aging.

Organisms require nutrients and other resources—oxygen, water, heat, shelter, other organisms, etc.—to survive and reproduce. They can acquire these resources directly from their environments or indirectly from others, most often their parents, and they have to allocate these resources, as well as their time, among a handful of tasks, including growth and development, reproduction, prevention and repair of bodily damage, external work, and storage. Prevention of bodily damage includes responding to and countering threats and stresses. And reproduction does not simply mean the energetic cost of having babies. It refers to all of the costs of producing and maintaining secondary sexual characteristics and finding mating partners, as well as bearing, raising, and providing resources for their offspring. In demographic terms, organisms use resources to increase survival and to increase fertility. Life history theory is a theory of the ways in which natural selection has shaped the physiological and behavioral mechanisms that regulate the acquisition and allocation of these resources over the life cycle.

The human life cycle can be divided into several more or less distinct stages—prenatal, infant (nursing), post-weaning dependent child, puberty and adolescence, sexual and reproductive maturity, and post-reproductive life. These stages are distinguished by differences in the ways we acquire and use nutrients and other resources. Natural selection has adjusted the timing of these stages as well as our activities in them. It has modulated the duration of gestation and of nursing, our overall growth rates and the growth of individual organs during childhood, the timing of puberty and the age at which we reach reproductive maturity, how

frequently we reproduce and how many children we have each time we do so, the age at which we cease reproduction, and the length of our post-reproductive lives (Stearns et al. 2008). Hormones mediate many of these life history “decisions” and so they play a central role in life history theory.

Each of these life history decisions involves tradeoffs or compromises. With respect to the duration of gestation, for example, there are advantages for fetuses to remain in utero, since the uterus provides a protected environment in which they can grow and develop. As fetuses grow larger, however, they become a bigger nutritional burden on the mother and suffer an increased risk of complications during labor and delivery. The timing of labor and delivery is apparently the optimal compromise between these two competing demands (Ellison 2001). The age at which we reach puberty and sexual maturity also involves tradeoffs. We need time to develop physically, psychologically, and socially to the point that we can bear and care for children. On the other hand, we need to become sexually mature and have the opportunity to reproduce when we are still young enough that we can have and raise our children before we’re likely to die. Yet again, there is a tradeoff between fertility and the survival of offspring that we discussed in Chapter 2, because the more children we have, the fewer resources we can allocate to each and the greater is their risk of dying before they reach reproductive maturity.

Presumably because they are regulated by pleiotropic genes, many life history traits are correlated among primate or mammalian species. For example, the duration of childhood or juvenility among primates is correlated with their life expectancy (Leigh 2001). There may be tradeoffs among suites of traits that evolve together. Moreover, as we shall discuss later, our life history strategies are not fixed but can change in response to environmental signals we receive during development. The range of life histories or other phenotypes that can be produced by organisms of a single genotype developing in a range of environments is known as their norm of reaction (Gilbert 2001). Natural selection does not act simply to optimize fitness in one specific environment. It modulates the norm of reaction to optimize fitness across the diversity of environments that a species has encountered during its evolutionary history. Our developmental flexibility and our ability to survive and reproduce in different environments may limit our adaptation to any one specific environment.

The human life cycle resembles the life cycles of other great apes, especially chimpanzees, but has a number of special features that presumably arose during the past 6 million years or so, since the time the hominin (human) lineage diverged from the lineage leading to chimpanzees (Robson et al. 2006). We have a slightly longer gestation period (9 vs 8 months) and lower rates of twinning than do chimpanzees. Women in many traditional societies nurse their babies for 2½–3 years, whereas chimpanzee mothers nurse for 4–5 years. Juvenile chimpanzees are able to acquire much of their own food by the time they are weaned and typically leave their mothers 2–3 years after weaning. We have a much longer period of childhood or juvenility, when children are no longer nursing but are still dependent on parents or others for food and survival. Because of this long period of childhood dependence, women typically have to care for several dependent children at the same time. Women have their first babies at a considerably older age than do chimpanzee females (19–20 vs 13–14 years). Because of

earlier weaning, women in natural fertility societies, i.e. in the absence of contraceptives or family planning, then have babies at shorter intervals than do chimpanzees (3–4 vs 5–6 years). Finally, although both women and chimpanzee mothers can have offspring until their early forties, we have much longer post-reproductive lives: chimpanzee females have life spans of 50–55 years while women have life spans of 80 or longer.

The special features of the human life cycle must have been shaped by the environments in which ancestral humans evolved, including among other factors the composition of ancestral human diets (Kaplan et al. 2003). Chimpanzee diets are rich in foods such as fruits and piths (the soft, fleshy material in the stems and branches of plants), which are relatively easy to obtain. Although we also eat fruits, they are a smaller component of our diets. We have evolved to eat a variety of energy-rich but difficult to acquire foods, such as nuts, seeds, roots, and meat. It takes a long time for children to acquire the skills needed to collect enough of these foods to be nutritionally self-sufficient. After they acquire these skills, however, adults can gather or hunt much more than they themselves need. Our long period of childhood dependence is made possible by the contributions of adults to the nutritional, educational, and social support of children.

There are controversies over how long it takes children to acquire the skills they need to become self-sufficient and over the relative roles of fathers, grandmothers, and other adults in helping to provision dependent children (Hawkes 2004). These aspects of child development and childcare may well differ in different societies. Despite these unresolved questions, this ecological perspective provides a plausible and attractive way of understanding the evolution of the human life cycle. Evolution of a prolonged childhood, which would have given children the opportunity to gain the knowledge and skills they needed to become self-sufficient, would have been accompanied by evolution of a longer life span, which gave adults more time to provision their dependent children. Long before the recent advances in medicine and public health that have extended our life expectancy, many of our ancestors who survived infancy and childhood went on to have long lives. Even in a population with a life expectancy of only 20 years, about a quarter of the population lives until age 50 (Coale 1974).

## 5.2 The causes of death change through the life cycle

Different stages of the life cycle are characterized by different patterns of disease and death. Recall that the major causes of death in infancy and childhood include congenital malformations and chromosomal abnormalities, genetic diseases, developmental defects, infectious diseases, and nutritional deficiencies. The high mortality of adolescent and young sexually mature men is due in large part to accidents, violence, and suicide. Deaths due to cardiovascular diseases and most cancers increase from about age ten onward but these diseases don't become the leading causes of death until around age 40, near the end of our period of reproductive maturity.

In addition to cardiovascular diseases and cancer, other noncommunicable diseases, including diabetes, chronic obstructive pulmonary disease, and neurodegenerative diseases, are also major causes of disability and death in the United States and other economically

developed countries. As developing countries go through the demographic and epidemiologic transitions we discussed in Chapter 2 and more people survive to reach the post-reproductive stage of the life cycle, these diseases of aging, which we shall refer to later as degenerative and man-made diseases, are bound to become even more important components of the global burden of disease (Omran 1971). These various classes of disease appear to have little in common. They affect different organs, they cause different kinds of pathological changes, and they produce different symptoms and disabilities in people who suffer from them. Understandably, different medical specialties have developed to care for patients with these various diseases and different advocacy groups have arisen to provide support for them. All of these clinically distinct classes of disease do, however, share one important epidemiologic characteristic: the incidence of and mortality from each of them increase with age. Life history theory provides a foundation for understanding many features of these and other diseases of aging.

### 5.3 What is aging?

Aging, or senescence, may be defined as a progressive, generalized impairment of function, resulting in a loss of adaptive responses to stress, an increasing probability of death, and, in many species, a decline in fertility (Kirkwood 1996). Although this definition sounds grim, we should remember that, at least in economically developed countries, aging is often accompanied by fewer responsibilities and increased leisure time, and that many older people continue to lead meaningful, productive, and rewarding lives even as they show some of the physiological signs of aging. Indeed, surveys suggest that older people are on average happier than younger ones. Aging itself is not a disease; it is a normal and expected—and hoped for—part of the life cycle. As the saying goes, growing old is a privilege. Nonetheless, as we grow older and enter the post-reproductive stage of the life cycle, we do have an increasing risk of developing and dying from a wide variety of seemingly unrelated diseases.

Why do organisms age? Aging did not evolve because aging and death make room for new organisms and so are good for the group or the species. This type of group selection is not a viable evolutionary process, because it would be undermined by selection for traits that increased individual survival and reproduction (Williams 1957). Moreover, aging did not evolve because the entropy, or disorder, of living organisms must inexorably increase according to the dictates of the second law of thermodynamics. In physical terms, living organisms are open systems that exchange matter and energy with their environments. As long as nutrients and energy are available, there is no thermodynamic reason why organisms could not survive and reproduce indefinitely. Nonetheless, if they live long enough, organisms of most species, even some bacteria, show evidence of aging. A number of invertebrate species do not show increases in age-specific mortality rates and so do not appear to age in nature (Rose 1991). We don't understand why these organisms don't age. For the moment, their lack of aging can only be seen as an intriguing curiosity. By and large, it seems that living organisms have evolved life histories that cause them to age.

Understanding the evolutionary biology of aging begins with a recognition that, as organisms go about their lives and interact with their environment, they expose themselves to risks of death from what biologists since Aristotle have called external or extrinsic causes (Aristotle c.350 BCE). External causes of death, which include natural disasters, starvation, and predation, are causes that cannot be eliminated by natural selection or by changes in life history strategies. Unpredictable natural disasters such as tsunamis and earthquakes kill organisms of all genotypes indiscriminately. The organisms that survive these disasters do so because of good luck, not because they have disaster-resistance genes. There may well be genetic variation in risk taking but it's hard to imagine that earthquakes select for risk-avoidance genes. Likewise, organisms have minimal nutritional requirements. Natural selection can enhance the efficiency of metabolism and can produce adaptations such as hibernation or dormancy that reduce metabolic rate when food is unavailable but it can't protect organisms from prolonged periods of drought or famine except perhaps by causing the production of inactive spores. And there are limits to the ability of natural selection to reduce susceptibility to predation within a population, because there are relatively few traits (speed and endurance, primarily) that might affect vulnerability to predation, and because predators coevolve with their prey. Adaptations that reduce predation, such as flying or burrowing, may involve such large changes in behavior or ecology that they lead to the formation of new species.

No matter what genotype they have, then, organisms will die at some rate from natural disasters, starvation, predation, or other extrinsic causes. As a cohort of organisms grows older, it will inevitably become smaller. In nature, most organisms die of these extrinsic causes before they have had a chance to age. Because organisms typically experience high mortality rates early in life, the age structure, or population pyramid, of most populations is heavily weighted toward younger organisms. Even though organisms of most species will show signs of aging if they live long enough, few have the privilege of growing old. And since relatively few organisms in nature experience aging, the characteristics of aging are unlikely to be the direct result of natural selection. Instead, they are almost certainly the incidental byproducts of selection for other traits, specifically selection for traits that increase reproductive fitness (Kirkwood and Austad 2000).

The rates at which populations die from extrinsic causes play an important role in shaping their life histories. Recall the tradeoffs between growth and development, reproduction, and bodily repair. Because of these tradeoffs, natural selection will cause populations that experience high mortality rates to evolve to reproduce early, such that members of these populations will reach reproductive maturity at ages when they still have a relatively high probability of survival. In contrast, populations with lower levels of mortality will, in general, evolve such that their members can allocate more resources to growth and development and delay reproduction (Stearns 1992).

## 5.4 The life history theory of aging

The life history theory of aging is based on the idea that the ability of natural selection to prevent death decreases with age. The evolutionary biologist William Hamilton was the first

person to point out clearly that the force of natural selection acting on age-specific mortality rates is proportional to the expected future contributions of this age group to their reproductive fitness (Hamilton 1966). Imagine an allele that causes death at a given age. If the allele causes death in infancy or childhood, before the onset of reproductive maturity, it will reduce fitness to zero and will be strongly selected against. As we saw in Chapter 3, the process of mutation-selection balance keeps such alleles at very low frequency. On the other hand, if the allele causes death after the end of our reproductive period, it will have no effect on fitness and will not be selected against. Between these extremes, there is a continuous decline in the ability of natural selection to prevent death at a given age. In brief, organisms age and die because of this decline in the ability of natural selection to prevent death.

Recall that the age-specific fertility rate for women declines to very low levels by age 45 or so. But our reproductive period does not end with the birth of our last child. Successful reproduction requires child rearing and perhaps even grandchild rearing. This extended period during which survival contributes to reproductive fitness has presumably slowed the decline in the force of natural selection and has contributed to the evolution of a significant life expectancy after menopause (Williams 1957). Nonetheless, there must be some age by which we have borne and raised our children and have helped ensure the survival of our grandchildren, and beyond which our survival has no evolutionary consequences—that is, beyond which death does not decrease fitness. At this age, the ability of natural selection to decrease mortality rates declines to zero.

The force of natural selection in preventing decreases in fertility also declines with age (Hamilton 1966). Changes in fertility are more difficult to analyze than are changes in mortality. Recall the tradeoff between fertility and offspring survival, between the quantity and quality of offspring. A decrease in fertility at one age may conserve resources that can be used to increase maternal survival and future reproduction. Moreover, as we discussed with regard to the demographic transition, fertility rates may be influenced by cultural norms as well as by natural selection. We shall focus on those aspects of aging that lead to increased mortality rather than those that result in decreased fertility.

If a population experiences high extrinsic mortality rates and evolves to have early reproductive maturity, the force of natural selection will decline rapidly with age. The success of a population in decreasing or preventing extrinsic causes of death will slow the decline in natural selection with age. Thus, the ecological interactions of organisms with their environments play a major role in shaping the life histories of their species. This evolutionary/ecological view of aging helps to explain many features of the comparative biology of aging. Among mammals, size and life span are closely correlated—large mammals live longer than small ones. We can understand this relationship because, in general, large animals are less subject to predation and so have reduced extrinsic mortality. Elephants, which are almost immune to predation, have exceptionally long life spans. Bats live longer than do other comparably sized mammals. Again, this makes sense, because bats can escape predation by flying and perching in inaccessible places. Perhaps for the same reason, birds live longer than do comparably sized mammals. And animals with extremely long life spans, such as some sea turtles and tortoises, have protective shells that greatly reduce their mortality from predation.

Among our close evolutionary relatives, humans have much longer life spans than do chimpanzees or gorillas. Recall that the life span of chimpanzees is in the fifties (Rose and Mueller 1998). Our life span has almost doubled during the roughly 6 million years since the hominin and chimpanzee lineages diverged. An attractive hypothesis to explain our increased longevity is that, as our ancestors evolved larger brains, developed the ability to work cooperatively in groups, and acquired the capacity for the transmission of cultural information, we became better able to hunt, to find food, and to avoid or kill predators. These skills decreased extrinsic mortality, which led to the evolution of delayed reproduction, which in turn slowed the decline in the force of natural selection with age. Our slow rate of aging and our prolonged childhood evolved in concert with our evolutionary ancestors' increasing success in warding off causes of death to which *their* ancestors would have succumbed. Again, our health and long lives are not the results of direct selection for longevity but are byproducts of selection for reproductive fitness. Our ancestors evolved to stay alive and healthy long enough to produce and raise their own children, and perhaps to help raise their grandchildren. What happened to them after that was of little evolutionary consequence.

## 5.5 Genetic causes of aging

There are several ways in which the waning power of natural selection might lead to aging. One early idea, proposed by the immunologist Peter Medawar, is the hypothesis of mutation accumulation (Medawar 1952). Medawar recognized that, as we have just discussed, mutations that increased the probability of death in childhood would be strongly selected against, whereas mutations that increased the probability of death in older people would not be. Deleterious mutations that act at older ages may simply accumulate in a population by genetic drift. The mutation accumulation hypothesis can account for the existence of some genetic diseases, such as Huntington's disease, which typically strikes people in their forties or fifties, but late-acting alleles seem unlikely to play a major role in aging. Most genes act early in development; few if any have no phenotypic effects until late in life.

Another hypothesis, that of antagonistic pleiotropy, was advanced by the evolutionary biologist George Williams (Williams 1957). Williams proposed that some alleles which had beneficial effects in childhood were detrimental in old age. Such alleles would spread in a population if their beneficial effects early in life outweighed their later harmful consequences. It is easy to imagine the existence of alleles with these properties. Williams' example was a hypothetical allele that increased bone calcification during development but led to increased arterial calcification later in life. Most genes are pleiotropic and their net effect on fitness must involve a tradeoff among all of their beneficial and deleterious effects.

More recently, the antagonistic pleiotropy hypothesis of aging has been formulated explicitly in terms of evolutionary life history theory. Tom Kirkwood, who is one of the architects of this view of aging, has dubbed it the disposable soma hypothesis (Kirkwood and Austad 2000). In today's idiom, it might be thought of as the recyclable soma hypothesis (Perlman 2008). Again, we have evolved mechanisms that allocate our finite resources of energy and time in ways that enhance our reproductive fitness. The utilization of these resources



necessarily involves tradeoffs between survival and fertility. Any genes that influence the allocation of resources must have pleiotropic effects: energy that is used for reproduction cannot also be used to prevent or repair bodily damage. Because resources are finite and because some must be allocated for other purposes, bodily maintenance and repair is in general not perfect. As a result, cells die, organ function declines, the ability to respond to stress is decreased, and the probability of death increases—in other words, we age. We don't have genes "for" aging. Instead, we have genes that regulate the allocation of energy to bodily repair and other purposes in ways that enhance fitness. Aging is the byproduct of this resource allocation. Natural selection has optimized our ability to transmit our genes to our children and grandchildren but once we have completed that task, our bodies are disposable and are recycled. Although he was writing with a different purpose, T. S. Eliot described the life history view of aging memorably: "And so each venture is a new beginning . . . With shabby equipment always deteriorating" (Eliot 1943).

## 5.6 Proximate causes of aging

From an evolutionary point of view, then, aging is a consequence of the evolved allocation of resources in ways that maximize our reproductive fitness even at the expense of somatic repair. What are the proximate mechanisms of somatic breakdown that require maintenance and repair? Our bodies are constantly undergoing somatic damage. Ions leak across cell membranes and have to be pumped in and out of cells; proteins become denatured and nonfunctional and must be degraded and replaced; DNA undergoes chemical damage (e.g. mutation) and has to be repaired; lipids suffer oxidative damage, etc. Many cell populations—epithelial cells such as those in the skin and gastrointestinal tract, red blood cells, and lymphocytes, among others—have limited life spans. These cells die and must be replaced. Finally, our bodies lose heat to the environment, and we need energy to overcome this heat loss and maintain our body temperature. All of these repair and maintenance processes require energy that might otherwise be used for reproduction or other purposes.

Much of the damage to somatic tissues comes from oxygen and glucose, two of the major substrates of metabolism. Both oxygen and glucose are chemically reactive molecules, which is presumably why they came to play essential roles in most living organisms. Nonetheless, their chemical reactivity can result in somatic damage. The spontaneous conversion of oxygen to superoxide radicals and other so-called "reactive oxygen species" leads to the oxidation of many cellular constituents. The oxidative deamination of cytosine residues in DNA that we discussed earlier is just one of several kinds of oxidative DNA damage that will result in somatic mutations and the loss of normal cellular function if this damage is not repaired before the DNA is replicated (Fraga et al. 1990). Reactive oxygen species can also oxidize and damage proteins and lipids, which in turn disrupts the structure and function of cell membranes. Energy must be used to remove and replace these oxidized lipids. Glucose reacts with free amino groups in proteins (particularly the N-terminal amino groups), resulting in glycation of these proteins. Glycation of collagen and elastin leads to covalent cross-linking and to the loss of elasticity seen in the skin of older people, and glycation of lens proteins may lead to



cataracts. But these are just the most obvious signs of the kinds of chemical damage that presumably impairs the function of other, more vital, proteins. Mitochondrial damage, especially deletions of mitochondrial DNA (Wallace 2010), and shortening of telomeres, the ends of chromosomes (Shammas 2011), can also lead to loss of cellular function.

In summary, our metabolic processes, which provide the energy we need for growth and development, for reproduction, and for work, are accompanied by damage to cells and organs, and some of the energy derived from metabolism must be used to minimize or repair this damage. Imperfect prevention and repair leads to the accumulation of bodily damage, which in turn leads to aging. Understanding aging as a consequence of our evolved life history strategy is consistent with and complements mechanistic theories of the aging process, which focus on the proximate mechanisms of the loss of bodily functions. An evolutionary understanding explains why we age and why organisms of different species age at different rates, and it may suggest interventions to decrease the rate of aging and postpone the onset of diseases of aging.

Given that aging results from utilization of limited nutritional resources for reproduction and other purposes rather than for somatic repair, it may seem paradoxical that calorie restriction increases longevity in many species (Bishop and Guarente 2007). One answer to this paradox appears to be that glucose and oxygen are responsible for much of the wear and tear of living. Calorie restriction may decrease the production of reactive oxygen species and so may decrease the rate of somatic damage, and may also divert energy from reproduction to bodily maintenance. The sex hormones testosterone and, to a lesser extent, estradiol decrease immune function and redirect resources to reproduction. Given this tradeoff between survival and fertility, it is not surprising that, in many species, including humans, castration increases longevity (Hamilton and Mestler 1969; Min et al. 2012). Less drastically, reproduction (number of children) appears to be negatively correlated with longevity in some human populations (Doblhammer and Oeppen 2003; Westendorp and Kirkwood 1998).

## 5.7 Somatic repair and the depletion of physiological capital

As life history considerations might lead us to expect, we have evolved a wealth of biochemical mechanisms to minimize and repair somatic damage. Natural selection has adjusted both the rate of somatic damage and the activity of our repair mechanisms. Our basal metabolic rate—our bodies' minimum caloric needs—is governed largely by the energy we devote to somatic repair. A significant amount of our basal or resting metabolism is used to pump ions across cell membranes and maintain the ionic composition of cells within physiological limits. Another substantial amount of energy is needed for protein synthesis and degradation. And part of our basal metabolism provides energy needed by the respiratory and circulatory systems to deliver oxygen and other nutrients to our tissues.

Antioxidant enzymes comprise an important group of bodily defense and repair mechanisms. Enzymes such as superoxide dismutase degrade reactive oxygen species and limit the oxidative damage these molecules would otherwise cause. The levels of superoxide dismutase and other antioxidants in mammalian tissues are correlated with longevity (Cutler 1991). Although these correlations do not prove a causal relationship, they are consistent with our

evolutionary understanding of aging. We also have enzymes that reverse oxidative damage to proteins and nucleic acids. Given the central role of DNA in cell function, it is not surprising that we have a myriad of mechanisms that maintain the integrity of DNA and minimize the production of mutations. The activity of DNA excision-repair enzymes is also correlated with longevity (Hart and Setlow 1974). Again, these mechanisms have not evolved to be perfect. Presumably, they have evolved to slow the rate of bodily damage to a level that optimizes our reproductive fitness.

Rates of aging are determined not only by the rates of bodily damage and repair, but also by the physiological capacities, or physiological reserves, that we accumulate during fetal and early postnatal development. For example, we are born with stem cells in many tissues. These stem cells can differentiate throughout life to replace cells that are damaged and destroyed by the mechanisms we have described. Eventually, however, our supply of functional stem cells becomes depleted and our ability to replace dead or damaged cells is decreased. Likewise, we are born with many more nephrons in our kidneys than we need to maintain physiological homeostasis. Indeed, we are born with two kidneys but we need only one to remain healthy. During life, nephrons become damaged and nonfunctional, and kidney function declines, but we do not develop signs of renal insufficiency until kidney function has decreased to perhaps 20% of its initial level.

An economic metaphor may help to clarify our understanding of aging. The endowment of stem cells, nephrons, and other resources that fetuses and infants acquire during development comprises what the economist Robert Fogel has called physiological capital (Fogel 2003). Physiological capital provides a reserve of physiological capacity that buffers us against the damage that occurs during life. Natural selection has provided us with sufficient physiological capital to stay alive and reproduce successfully in the face of the expected demands for this capital. Eventually, as our physiological capital becomes depleted, we get sick and die. The rate at which we age is determined by the amount of physiological capital we accumulate early in development and the rate at which this capital is depleted as a result of the physiological damage we suffer later in life.

From a public health perspective, one of the most common and debilitating deficits in the elderly is a loss of balance and an increased risk of falling. Falls are not only physically damaging but fear of falling may cause older people to become less active and more socially isolated. Our sense of balance depends on the proper functioning of the otoconial organs, the utricle and saccule, in our inner ear. Hair cells in these organs have cilia that are embedded in an extracellular matrix made up of otoconia, macromolecular complexes containing calcium carbonate crystals bound to glycoproteins. Otoconia are gravity receptors. They are heavier than extracellular fluids. When they move in response to gravity they displace the cilia, which leads to changes in the neuronal output of the otoconial organs. Our utricles and saccules contain several hundred thousand otoconia, which are laid down during fetal development before these organs are functional. Over time, calcium is leached from the otoconia into the surrounding extracellular fluid and the otoconia fall apart. Because these damaged and non-functional otoconia can't be replaced, we lose our sense of balance. Changes in otoconial function during the life cycle exemplify the concept that the impairments of aging result from

the balance between the accumulation and depletion of physiological capital. Unfortunately, we don't yet know how to modulate either the accumulation of otoconia during development or their rate of loss during life (Mason 2011).

Different people manifest the effects of aging differently. Some develop cardiovascular failure, some show signs of respiratory insufficiency, some suffer cognitive loss, and some acquire other deficits or disabilities. These differences are due in part to environmental factors, such as occupational hazards, nutrition, or behavior, that may increase damage to one specific organ or organ system. In addition, genetic risk factors increase the susceptibility of different people to different diseases. These genes may affect the accumulation or depletion of specific types of physiological capital. Somatic mutations may play an important role in the development of age-related diseases. For the population as a whole, however, aging seems to involve a more or less simultaneous loss of function of many organs and organ systems. This simultaneous wearing out of many physiological systems can be understood in terms of what Richard Dawkins has called the principle of animal design (Dawkins 1995). Natural selection is unlikely to produce kidneys that can sustain us for 150 years if our hearts are likely to stop functioning after age 80. Again, there are tradeoffs in the use of limited resources; energy that is used to develop physiological reserves that will never be needed can better be used for other purposes. Natural selection presumably adjusts the activities of antioxidant defenses, DNA repair enzymes, etc., so that different types of unrepaired somatic damage all contribute to aging and disease. An evolutionary view of aging helps us understand why older people tend to suffer from multiple ailments, or comorbidities. It also helps us appreciate that preventing or curing the major age-related diseases will not lead to immortality. People who don't die from one disease of aging are likely to die of another before very long. Finally, it helps us realize why the multiple parallel pathways that contribute to somatic breakdown—oxidative damage, mitochondrial dysfunction, etc.—have made it difficult to identify the relative importance of specific causal mechanisms in aging.

In short, evolutionary life history theory provides a firm foundation from which to understand the important diseases of aging. An appreciation that aging results from our evolved life history strategies, from the balance between the accumulation and depletion of physiological capital, provides a framework around which to design interventions to slow the aging process and postpone the onset and progression of diseases of aging.

## 5.8 Plasticity in rates of aging

Although our aging may be inevitable, the human life span and the time course of aging are not fixed. During the past century, the life expectancy of 50-year-old people in the United States has increased by 10 years, from 21 years in 1900 to 31 years today. There are several reasons why life expectancy, even of older people, is continuing to increase. Presumably because of better maternal health and nutrition, infants are born with more physiological capital and so have healthier or more resilient cells, tissues, and organs. Better nutrition and fewer serious infectious diseases in infancy and childhood preserve our physiological capital and slow its decline. Thus, people are entering adult life better able to respond to or repair the insults

that lead to the diseases of aging. Environmental hazards such as smoking are major causes of somatic damage. The decline in smoking over the last 50 years has contributed significantly to our increased life expectancy (Peto et al. 2000; Stewart et al. 2009). Older adults today have fewer chronic conditions and get these diseases later in life than did adults a century or even a generation ago (Fogel 2003). This postponement of the onset of diseases of aging is probably due both to greater reserves at birth and to slower declines during life.

## 5.9 Developmental origins of health and disease

Plasticity in rates of aging is part of a broader plasticity in our life history strategies and adult phenotypes. Recall that natural selection shapes organisms' developmental processes in ways that optimize their norm of reaction, their fitness over a range of environments. Developing organisms receive signals or cues about their environments. Zygotes receive epigenetic marks on the genomes they acquire from their parents at the time of fertilization, and fetuses receive nutritional and endocrine signals from their mothers throughout their development. These signals presumably convey information about the mother's health and nutritional status, as well as about other aspects of the mother's environment. They may cause changes in development that prepare the fetus for the environment it will experience after it is born or possibly for the environment it is likely to encounter later in life (Bateson 2001).

Just as extrinsic mortality rates have shaped the life histories of species over evolutionary time, anticipated mortality rates may modulate individual life history strategies during development. Female fetuses and infants who receive information suggesting that they will grow up in a harsh or dangerous environment, where the expectation of a healthy life is short, develop in ways that lead to earlier menarche and tend to have their first children at earlier ages (Chisholm 1999; Nettle 2011; Sloboda et al. 2009). The environmental signals that lead to early puberty and early reproduction may be nutritional, endocrine, or psychosocial, and they may act in utero or in childhood. The physiological changes associated with early menarche presumably involve epigenetic changes in gene expression that lead to early activation of the hypothalamic-pituitary-ovary axis. Increased investment in early reproduction is accompanied by decreased investment in physiological capital and somatic maintenance, and so results in an increased risk, or earlier onset, of diseases of aging. Even though this life history strategy of early puberty and early reproduction is associated with an increased risk of adult disease, it is probably best understood as an adaptive response that evolved because it optimized reproductive fitness in stressful or dangerous environments, where it may have been risky to postpone reproduction. This phenomenon appears to be an example of what might be called epigenetic antagonistic pleiotropy, in which the benefits of early reproduction outweigh the costs of early aging.

Some of the responses to early developmental conditions are harder to interpret. Most nephrons are formed in the last trimester of pregnancy. Babies who are born premature or who have low birth weight because of intrauterine growth retardation have a reduced number of nephrons at birth and so are at increased risk of developing chronic kidney disease and hypertension as they age and lose renal function (Hershkovitz et al. 2007). Reduced nephron number may be part of an evolved life history strategy to conserve resources for reproduction

rather than invest in physiological capital. Alternately, it may simply be the bad outcome of developing in an unhealthy intrauterine environment. In either event, the relationship between nephron number at birth and the risk of renal disease in adult life highlights the importance of physiological capital in prolonging health.

While our developmental plasticity must have evolved because on balance it increased the reproductive fitness of our ancestors, this plasticity renders us susceptible to environmental toxins that alter our life history strategies. There is currently much concern about the possibility that endocrine disruptors, exogenous compounds that block or mimic the actions of hormones, are causing early puberty and are increasing the risk of disease in adult life (Schug et al. 2011). Since these agents were not part of our ancestral environment, our responses to them are pathologies, not adaptations.

The epidemiologist David Barker and others have collected a wealth of epidemiologic evidence documenting that babies who are undernourished during fetal development or early infancy are at increased risk of developing diabetes, cardiovascular disease, and other diseases in adult life (Barker 2004). Barker's work has led to the creation of a new field, developmental origins of health and disease, which is devoted to exploring the relationships between early development and adult disease (Gluckman et al. 2007; Gluckman et al. 2010). These relationships are complex and hard to study, especially in humans, and our life histories are so different from the life histories of model organisms that research on these organisms may not be directly applicable to us. The most common measures of fetal development, gestational age and birth weight, are probably not good proxies for the nutritional or endocrine cues that actually affect our life histories. We are just beginning to identify the relevant signals and the developmental periods during which they act, and the epigenetic mechanisms by which they modify gene expression, hormone secretion, and development (Drake et al. 2012).

Barker and Nicholas Hales have suggested that the increased risk of diabetes among people who were undernourished early in development is a tradeoff for enhanced fetal and neonatal survival (Hales and Barker 2001). Specifically, they suggested that a poor nutritional environment during development leads to insulin resistance, which slows growth and preserves nutrition for brain development and reproduction but which subsequently increases the risk of developing diabetes. If their hypothesis is correct, the physiological response to early environmental deprivation would be another example of epigenetic antagonistic pleiotropy.

The risk of developing diabetes and cardiovascular disease is particularly great for people who are small at birth and infancy but who subsequently gain excess weight in childhood. Increased adiposity exacerbates insulin resistance and may also increase inflammation in these "thin then fat" people (Hales and Barker 2001). While the pathophysiological mechanisms are still being worked out and our current understanding is far from complete, these observations have called attention to the problems that can result from a mismatch between the environment a fetus or infant experiences during development and the environment it then encounters later in life (Gluckman and Hanson 2006). Changes in food supplies in economically developing countries and among people who migrate from developing to developed countries may be exacerbating this mismatch and may be contributing to the increasing prevalence of diabetes and cardiovascular disease in these populations (Wells 2010).

