Chapter 1

Evolution: Death's Unifying Principle

> We should also recall, as if we needed reminding, that we are mortal and limited, and thus should remember that the old myths of unrestricted curiosity and the corruption of power are not necessarily fables.
>
> —Simon Conway Morris, *Life's Solution: Inevitable Humans in a Lonely Universe*

> Normality seems to have nothing to do with it, for the fact that we will all inevitably die in a few score years cannot by itself imply that it would not be good to live longer.
>
> —Thomas Nagel, *Mortal Questions*

> The machine, mon ami, wears out. One cannot, alas, install the new engine and continue to run as before like a motor car.
>
> —Agatha Christie, *Curtain: Hercule Poirot's Last and Greatest Case*

All living things have their own ways of dying or not. I describe these ways in the appendix, but *The Evolution of Death* is primarily concerned with death in *Homo sapiens*—our death. If we are ever to understand death, it will be because we see it as part of life—as evolving. Science got it wrong several times in the past, but the consequences of death's resuscitation, its reinstallation in life, for culture and civilization will be enormous.

DEATH EVOLVES!

In the last few hundred years, human beings have created an environment in which death has been delayed as a result of all sorts of improvements:

sanitation, nutrition, medicine, and so on. Those who most profited from these changes have lived to tell the tale. And their survival and reproduction has shaped the evolution of our death. Consequently, individuals remain young longer and delay aging to their later years. Indeed, so-called natural or age-dependent human death now comes later than at any time in the past.

One struggles vainly to isolate a single cause of death's evolution. For example, levels of dietary sodium and genes both influence each of the age-related biological measures of declining cardiac function, including heart rate, blood pressure, and arterial stiffness. Effects of environmental and genetic factors on aging, dying, and death may be indistinguishable, and particular environments seem to produce phenocopies (that is, environmentally induced mimics of mutations). For example, in model systems, the effects of caloric restriction on enhancing longevity are identical to single gene mutations that increase life span from 30 percent to a doubling or more.[1] The environmental effect set off by reducing the number of calories in the diet converges with the effect of genes encoding members of the insulin-like glucose-metabolism pathway. Like life, death is a facet of underlying continuity, endlessly moving and evolving.

The scale of death's recent evolution is also difficult to grasp, and accepting it may require a thorough reorientation toward life. Instead of imagining death as the antithesis of life, death must be appreciated as an evolving part of life and an adaptation to life. Life must also be seen differently, namely, as incorporating the various aspects of death, such as exchange, feedback, turnover, and regulation. Indeed, death's major features, it turns out, create life as we know it, and even make life possible!

One might think, naively, isn't it ironic that death has evolved toward the accumulation of resources, the prolongation of youth, and the extension of life in succeeding generations? But the irony disappears upon reflection. When we die of old age, it is not because we have failed prematurely to utilize our inborn resources. Those resources—in particular, our stem cells—are invested throughout our lifetime. We die because these resources are exhausted. We die because hardly anything remains (for example, of our stem-cell populations) capable of supporting further life. But the downstream movement of death is a direct consequence of our upstream addition of resources that prolong youthfulness and hence life. In the future, as long as we continue to shape our ecological niche toward longevity, human beings will be born with greater and greater resources and hence increased longevity. It is widely acknowledged that human beings are generally living longer today than ever before, but death will continue to optimize, and as it approaches its apotheosis, death will all but disappear!

Chance, of course, also enters the equation of life,[2] in the sense of reactions that are probabilistic as opposed to deterministic, and constraints on intrinsically stochastic fluctuation and feedback rather than mere alternate

pathways and unspecified ranges of variation. Hence chance, along with the environment and genes, enters equations for the accumulation and availability of resources, accounting for the variability of life span.

Thus, death is a part of life. Death evolves when living things accumulate resources, when genes and other hereditary influences provide the pathways that make those resources available, the environment makes them accessible, and chance decides whether or not a resource will be there when needed. Death is subject to natural selection, changing over generations under the auspices of contingency and opportunity. By coming later in life, after the exhaustion of resources, death exhibits the exquisite integration of structure and function peculiar to life. And, hence, death is adaptive. Through its evolution, death increases fitness, emerging from and enhancing reproduction, like other aspects of life. Indeed, we still die, but evolution has made death operate more efficiently and economically than at any time in the past—and death is still evolving.

FALSE CLUES: WHERE SCIENCE GOT IT WRONG

Scientists function to provide worldly solutions to problems and favor numbers and equations over mere words. And scientists are supposed to be sufficiently disinterested when it comes to death to perform their function.

The Nobel Prize–winning zoologist/immunologist and author, Peter Medawar, for example, had no truck with terms pirated from the vernacular, insisting instead on a working understanding. From his vantage point, the terms "life" and "death" "used in scientific contexts [were] far removed from those [contexts] that might arise in common speech . . . [such as] whether the condition of the possible [organ] donor is reversible or not."[3] But even scientists willing to take on eternal verities frame aging, dying, and death within a canonical mold: we die because living things have always died.[4] Thus, we die at the behest of statistics, of a species' finite life span, of killer genes, killer environments, or entropy and the laws of thermodynamics. But do we?

Chapter 1 examines the objectivity of these scientific truths. Several questions are raised in the form of "Do we die at the whim (command, behest) of . . . ?" But to all these questions, the answer is resolutely no. The rejection of these "objective" possibilities ultimately places death on its one firm basis, namely, life.

Do We Die at the Whim of Statistics?

Thomas Robert Malthus (1766–1834) should be credited with making an early effort to put a scientific face on the statistics of death. His 1798 *An Essay on*

the Principle of Population (largely a polemic on the necessity for appropriation and uneven distribution of wealth, a diatribe against Mr. Pitt's Poor Laws, the parish system, and enclosure of the commons, and a mocking critique of notions of physical immortality) argued "that the power of population is indefinitely greater than the power in the earth to produce subsistence for man," and "in no state that we have yet known has the power of population been left to exert itself with perfect freedom."[5] Therefore, populations are held in check, frequently, but not necessarily, at their subsistence level. According to Malthus, human populations are constrained both positively (preventively), for example, by marriage, virtue, and other moral constraints, and negatively (destructively), for example, by contraception, abortion ("improper arts to conceal"[6]), and premature death. Specifically, the "lower classes . . . suffer from the want of proper and sufficient food, from hard labour and unwholesome habitations . . . [to which] may be added vicious customs with respect to women, great cities, unwholesome manufactures, luxury, pestilence, and war."[7] Later, in *A Summary View of the Principle of Population,* Malthus added to the list of negatives the "whole train of common diseases and epidemics . . . infanticide, plague and famine."[8]

Charles Robert Darwin (1809–1882) "happened to read for amusement Malthus on *Population,* and being well prepared to appreciate the struggle for existence which everywhere goes on . . . [was] at once struck . . . that under these circumstances favourable variation would tend to be preserved, and unfavourable ones to be destroyed."[9] Alfred Russel Wallace (1823–1913), the "other" discoverer of natural selection, admits to a similar "coincidence."[10] But candor aside, Darwin and Wallace were compelled to acknowledge their debt to Malthus if only because his pamphlet was widely read. His doctrine might also have been broadly accepted in Britain, if not elsewhere, as Daniel Todes points out: "[I]t would not be surprising if Darwin's contemporaries, especially those outside of the British cultural context, associated his struggle for existence with specifically British, bourgeois, or Malthusian values."[11]

Of course, Darwin and Wallace were less interested in what kept populations in check than in what unleashed the origin of new species. Thus, Darwinism took Malthus's notion of negative checks onestep further, implying that some organisms were selectively squeezed out or killed while others survived because of their advantageous morphology. Pasted together, Malthusian constraints and Darwinian selection became, in essence, a theory of death creating room at the top, or space for the evolution of improved species. But is this synthesis incontrovertible?

Were death to serve the evolutionary function of creating wiggle room for favorable variants, aging and dying would be especially advantageous in species confronting complex and changing environments simply because the survival of these species might depend on variant organisms that happen to be better adapted to new circumstance than run-of-the-mill organisms. Indeed,

sexual reproduction itself seems specialized for producing new varieties of organisms, since sex promotes the mixing of genes as a result of (1) recombination between homologous chromosomes, (2) reshuffling originally maternal and paternal chromosomes during the formation of sex or germ cells, and (3) randomly combining germ cells during fertilization. But reshuffling is at least as likely to destroy favorable combinations of genes as to promote fitness interactions, and the results of recombination in the HIV-1 retrovirus, where recombination is frequent, "challenge hypotheses about the evolution of recombination,"[12] suggesting instead that recombination (or template switching) functions in the repair of single strand breaks. Recombination, thus, may be a consequence of and not the cause of evolution.

A second problem is that Darwinian evolution by natural selection requires a reproductive advantage for the individual being selected, and genes promoting the death of the individual would not seem to promote the individual's reproduction, especially if death came before reproduction! Even selfish genes do not bite the hand that passes them to the next generation.

Ultimately, the notion of death offering an advantage founders on the rocks of the fossil record. In fact, there isn't any—or perhaps just very little—room at the top! While human history may well be a tale written by victors, evolutionary scenarios deciphered from the fossil record are tales written by surviving remnants—castaways, outcasts, refugees, and emigrants—left in the wake of cataclysms or isolating processes.

It is not death, after all, that makes way for variation, but changed ecological circumstance that gives existing variants a chance to emerge. Historically, the species that has been most successful in one era (has cornered the market or found an evolutionarily stable strategy) is a dead end in the next era. Such species are more likely to be too specialized to adapt to new circumstance, even with all their variants thrown into the mix. On the other hand, a peripheral and generalized species, possibly highly dispersed as well, is the one likely to evolve and give rise to new species when the environment changes—for example, mammals as opposed to dinosaurs beyond the Cretaceous-Tertiary boundary.

Ultimately, the tree of life would seem to grow by Lenin's rule of revolutions: one step forward for two steps back. Death may clean up the detritus of history, but it does not advance history. One does not die at the behest of population dynamics, and death is not adapted to making room at the top.[13]

Do Species Have a Finite Life Span?

For us, a life span—the interval between fertilization and death—is frequently confused with a lifetime—the interval between birth and death. Be that as it may, the question here is whether an average or even a maximum lifetime is

determined in our species. In other words, is life span or lifetime a species-specific characteristic or merely a circumstantial characteristic, possibly species-typical but without any causal connotation of built-in limit?

Life spans are described in several ways (mean, median, mode, etc.) and are visualized in different ways. For present purposes, the most convenient way of illustrating life spans is as survivorship distributions, the rate at which a cohort (all the organisms starting their life span at the same time) dies out. Survivorship curves demonstrate the totally different ways cohorts of different species die out while living in their different environments and making their living in different ways.

The conjunction of the surviving number of organisms in a cohort (along the Y axis) and the period of time (along the X axis) until the last member of the cohort is dead is plotted in a survivorship distribution. In the distributions shown in figure 1.1, the time axis is calibrated in fractions of a life span (centiles or hundredths of a lifetime) in order to facilitate comparisons between species with differing life spans.

The three species with survivorship distributions plotted here are *Homo sapiens,* represented by a 1910 cohort of white males (open squares), a ubiquitous, microscopic rotifer, *Proales decipiens* (closed triangles), and the fruit fly *Drosophila* (closed diamonds) captured in the wild.[14] The distributions illustrate how death erodes each cohort under natural conditions (as opposed to the artificial and virtually sterile conditions of the laboratory).[15]

Each of the three distributions has an inverted S shape, beginning and ending with more nearly flat portions connected by a smoothly curving diagonal portion. The flattened portions at the beginning indicate how long members of a cohort live before death begins to take its toll, while the flattened portions at the end indicate how long members of a cohort live before death completes its job in old age. The curvature in the middle portions is a function of how rapidly death descends upon the cohort between an initial delay and a late deceleration.

Were species-determination to play no part in influencing individuals' life span and were death entirely a random event, the survivorship distribution would fall off at a constant rate throughout the distribution. Alternatively, were species-determination the sole influence on individuals' life spans, the survivorship distribution would be maximal and level at first, and then would drop precipitously down to zero at the age when individuals reach their species-specific life span. Of course, in a state of nature, or even in a laboratory, organisms may die from vague causes that distort a distribution, including statistical error in collecting data and random deviation from the ideal. These nebulous causes must be accepted without clouding a view of the principal causes of death.

The curve for wild *Drosophila* comes nearest the prediction for death as a function of random accident with constant probability, but even this curve

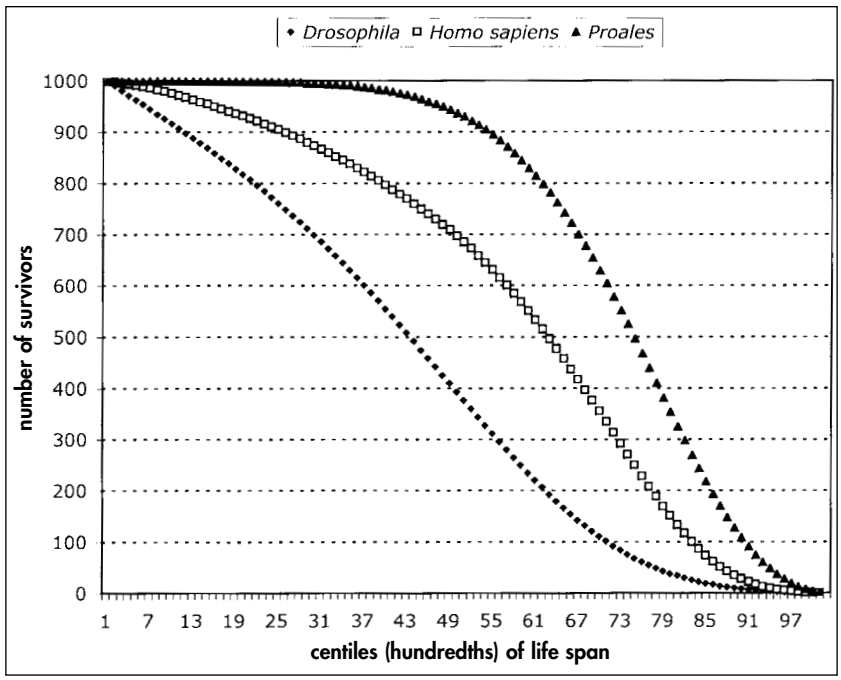

FIGURE 1.1. Survivorship distributions for comparable life spans. (Curves drawn from data in Pearl, 1924, 376–77, table 112.)

bends slightly at the beginning and levels off conspicuously as the cohort's membership approaches zero. *Drosophila* raised under laboratory conditions produce survivorship distributions virtually identical to those shown here for human beings, suggesting that animals in nature suffer from a number of diseases that are not present under conditions of domestication.

In contrast to the *Drosophila* distribution, the distribution for the survival of the tiny rotifer, *Proales,* comes nearest the prediction for death as a function of a species' life-limit, proceeding nearly horizontally at first before dropping off dramatically. The survivorship distribution for *Homo sapiens* is intermediate: somewhat flat at the beginning before dipping and flattening at the end as the death rate slows.

Thus, while random accidents may play a nearly constant role in killing off *Drosophila* in the wild during most of their lifetime, accidents play a minor role in killing off *Proales* and an intermediate role in killing off *Homo sapiens.* On the other hand, the life span of *Proales* would seem very much more biologically determined than the life spans of *Drosophila* and *Homo sapiens.* The tiny rotifer would seem, somehow, to die on a schedule, with the absolute

duration of its life span (that is, its life-limit) strongly determined. The duration of a life span in *Homo sapiens* would seem less biologically determined than *Proales* and that of *Drosophila* would seem least determined of the three.

Of course, biological determination is influenced by many things, from genetics to epigenetics, from nuclear genes to environmental effects, and one must always bear alternatives in mind, as well as their possible interactions, when speculating on biological determination. But, mutations altering life span–determination in the three species would be expected to alter the survivorship distributions differently to the degree that genes alone influence biological determination. Thus, in the case of *Proales,* mutations affecting the life span might delay the onset of death, thereby extending the interval of life. In *Drosophila,* mutations affecting the lifetime might create more resistance to disease, pushing the survivorship curve upward (rounding the straight line).[16] In *Homo sapiens,* different mutations affecting the lifetime might change both parameters: push the survivorship curve upward and extend its limit.

Actually, selection for eggs, but not mutants as such, of young rotifers extends life span,[17] and gerontologist Caleb Finch suggests that rotifers "give a model for the relationship between specific cytoplasmic determinants during oogenesis and the epigenetic control of senescence."[18] On the other hand, mutations, rather than epigenetic controls, would seem to be involved in the lengthening of lifetime in the roundworm, *Caenorhabditis elegans*, when too much of the protein Sir2 (silent information regulator 2) is produced in mutants.[19] The evidence in *Drosophila* and mice is, however, ambiguous, since the lengthening of lifetime in fruit flies may be spontaneously reversed, possibly by affecting development, and, in mammals, genes affecting life span also influence growth and cause cardiopulmonary lesions as much as influence aging.[20] The effects of mutants on the average human life span are simply uncertain, and gerontologists Leonid Gavrilov and Natalia Gavrilova warn that "the age-dependent component of mortality . . . is historically stable."[21]

The species-specificity of biological "destiny," thus, would seem to work differently in *Homo, Proales*, and *Drosophila.* These organisms evolved under different circumstances and with different histories, producing different overall strategies for life, for survival, reproduction, and death. If one ignores for the moment all the complexity that goes into evolution, notably fecundity, the rotifer would seem narrowly determined to get it over with, while the fruit fly takes its chances, and the human being hedges its bets.

In effect, genetic, epigenetic, and environmental effects all come to bear on biological determination and one cannot exclude any of these influences. One could do little to effect change in the rotifer's lifetime without changing its species-specific biological determinants (whether genetic or epigenetic); the fruit fly's lifetime could be changed most rapidly by changing its environmental exposure or its intrinsic fragility (that is, eliminating the kinds of events that kill it or render it vulnerable to these events); the human being

would fall somewhere between, subject to both rapid change due to local circumstance and long-range change due to changing its biological nature genetically or epigenetically. In any event, unlike *Proales,* our species-specific determinants are not our main executioner. The life span of *Homo sapiens* may, indeed, be species-typical (or what are statistics for?), but neither an average nor a maximum would seem species-determined.

Do We Die at the Command of Killer Genes?

Ever since 1953 when James Watson and Francis Crick succeeded in reducing genetic continuity in deoxyribonucleic acid—better known as DNA—to the simple game of matching base pairs (adenine [A] to thymine [T] and cytosine [C] to guanine [G] or A → T; C → G), genetics has dominated the life sciences. Indeed, reducing biological complexity to its genetic components is the predominant objective, if not the only objective, of most research in the life sciences and the *raison d'être* of the multinational, multibillion–dollar Human Genome Project.

But genes are not the only things that influence heredity. We are constantly learning about other influences, from mitochondria to DNA methylation, all of which fall vaguely and loosely under the umbrella of *epigenetic controls,* reprogramming or specific changes to the *epigenome.* Indeed, in addition to "the major type of DNA modification . . . [via] the methylation at cytosines, there are multiple modifications associated with chromatin . . . [in which] hereditability has been demonstrated only in rare cases."[22] Gerontology is, however, so deeply imbued with biology's genetic paradigm that virtually any other approach to solving the problems of aging, dying, and death is rejected and tarred with the brush of holism (antireductionism) if not vitalism.

What is it, then, that genes could do to influence our life span, our aging, our dying, and our death? In general, genes work through their products, frequently ribonucleic acid (RNA) and hence proteins. Even the most far-reaching genes, those that determine hereditary traits, have their most immediate effects within the cells that produce the gene's coded RNA and resulting protein. In turn, the products of cells operate on tissues, organs, and organ systems by interactions, through induction and transduction pathways. The products of genes may operate at one stage of development or throughout the course of a lifetime, in everyday upkeep, and/or in response to challenges. But in every case, genes are thought to exert their influence through some effect on cells or their products, and cells then mediate the indirect effects of genes.

How, then, could genes intervene in life spans and cause aging, dying, and death? Ordinarily, cells in many tissues throughout the body undergo turnover: differentiated cells die and are replaced by new cells. At one time, one would have said that the cells die in the course of differentiation, for example, in the

case of the keratinizing epidermis, but today, cells are said to die through programmed cell death (PCD) involving one or another mechanism: apoptosis, in which single cells die and are digested by so-called macrophages; and autophagia, in which groups of cells dissolve or harden (i.e., tan) under the influence of their own lytic enzymes or denaturing mechanisms. Specifically, genes said to be involved in aging are widely thought to operate through cumulative effects on cell loss over time, especially cell loss implicated in disease (for example, neurodegeneration, retinal degeneration, cardiovascular disease) and increased frailty or vulnerability to a variety of diseases.[23] On the other hand, genes said to be involved in life's prolongation are thought to operate by attenuating the loss of cells. Thus, for example, "long-lived genetic mutants such as the $p66^{sch}$ knockout mouse are typically less prone to stress-induced apoptosis [than normal mice]."[24]

Aging, Dying, and Death Genes

The possibility of genes governing aging, dying, and death has a number of permutations. There would seem to be no end of genes that influence life span.[25] The gerontologist Tom Kirkwood has proposed, under the title of the "disposable soma" hypothesis, that organisms, especially long-lived, complex organisms, employ considerable numbers of genes in regulative roles supporting growth, development, and maintenance. Aging results from the accumulation of irreparable defects in these genes and hence in the failure of cells to maintain and repair the soma (body) in the wake of stress and environmental hazards.[26]

The authors of *Successful Aging,* John W. Rowe and Robert L. Kahn, are slightly more circumspect:

> [T]he strongest influence of heredity on aging relates to genetic diseases that can shorten life, such as numerous forms of cancer and familial high cholesterol syndromes (which lead to heart disease). . . . Still, however, heredity is not as powerful a player as many assume. For all but the most strongly determined genetic diseases, such as Huntington's disease, MacArthur Studies show that the environment and lifestyle have a powerful impact on the likelihood of actually developing the disorder. . . . Genes play a key role in promoting disease, but they are certainly less than half the story.[27]

The bio-gerontologist Aubrey de Grey goes further: "Genes are not responsible for aging. Genes are responsible for defending us, to a greater or lesser degree depending on the species, AGAINST aging."[28] Moreover, according to the gerontologists Jay Olshansky and Bruce Carnes, "[t]he requirement that death genes become activated at ages beyond the reproduc-

tive years means that evolution could not give rise to them."[29] And the science writer Stephen Hall quotes the gerontologist Leonard Hayflick, the grandparent of all cell-aging studies, as insisting that "[t]here are no genes for aging . . . I'll say that categorically, and I'll defend it despite what you have heard."[30] Natalia Gavrilova and Leonid Gavrilov state equally categorically that "many of these 'self-evident' assumptions (for example, the normal life span distribution law, and the notion of an absolute limit to longevity) are simply unsound when tested . . . and an absolute upper limit to longevity appears not to exist."[31]

The obvious problem with genes for aging, dying, and death is that they would seem to offer no adaptive advantage to individuals possessing these genes, and, hence, would have no way of evolving into stable parts of the genome. Modern genetics may attempt to rescue death genes as hitchhikers or deceivers, but the attempts are unconvincing. Deleterious genes may get into the genome by hitchhiking—going along for the ride, so to speak—were they closely linked to adaptive genes, but no such hitchhikers are presently known. Moreover, genes getting into the genome by deception might enhance the fitness of the individual at one stage of life only to diminish fitness at another stage, but why would the same gene have opposite effects at different times of life?

The evolutionary biologist George Williams's "theory of antagonistic pleiotropy" is a theory of genetic deception. "Pleiotropy" refers to genes with more than one effect, while "antagonistic" implies that these effects are contradictory. The theory would have the pleiotropic effects occurring serially, and thus the effects follow one another. Williams suggests that a net gain in Darwinian fitness would accrue to organisms were genes with favorable effects prior to or during the reproductive period of a lifetime to have deleterious effects in the late or postreproductive period.[32] Attributing opposite effects to genes for the sake of explaining aging would seem circular, but many gerontologists find the theory of antagonistic serial pleiotropy attractive and continue looking for once felicitous genes that become deleterious and cause aging, dying, and death late in life. Certainly, all of biology will take notice if these gerontologists come up with some such genes, but, at present, the search has been fruitless.

The Sad History of Longevity Genetics

Genetics' importance for biology begins long before Watson and Crick with the "rediscovery" of Mendel's laws of hereditary at the beginning of the twentieth century. Since then, biologists have been divided between those who attempt to analyze life as something determined by genes and those who concede that the mixture of genetic and environmental factors are inseparable.[33] (Those who suggest that non-Mendelian heredity may also play a role may be

making a comeback,[34] but those who might have argued in favor of purely environmental determinants of life have long since been drummed out of the profession.) Of course, a great deal of the debate between members of the two camps hinges on exactly what one means by genes, but the definition of genes has only become more confused and controversial with the passage of time.

For twentieth century evolutionists, the foremost problem that Mendelian genetics was supposed to solve was how Darwinian evolution by natural selection worked at the level of genes.[35] But, for the first quarter of the twentieth century, Mendelian genetics failed to illuminate evolution at all. Many of Darwin's most loyal supporters took different and competing sides of the issue. The embryologist-turned geneticist Thomas Hunt Morgan and his coterie in the "fly room" laboratory at Columbia University became the strongest adherents to the strict Mendelian precept of particulate inheritance. Morgan examined qualitative inheritance and largely ignored natural selection's requirement for the inheritance of small, quantitative changes. The Dutch botanist Hugo DeVries showed how a rare, large, hereditary change, called a *mutation*, could create virtually new species in a single step, but his discovery was so antithetical to the gradualism of natural selection that it threatened to scuttle Darwinism altogether. The equilibrium discovered by Goddfrey Harold Hardy and Wilhelm Weinberg, and known as the Hardy/Weinberg law, moreover, demonstrated that infrequent mutations could have only minimal effects on populations. Meanwhile, William Bateson, the Cambridge zoologist and "apostle of Mendel"[36] who coined "genetics" but not the "gene,"[37] floated a version of Mendelian factors at odds with both Morgan's chromosomal theory and the notion of quantitative inheritance spawned by the London biometrician, Karl Pearson.

Among the early geneticists, Pearson was most interested in longevity and might have kick-started the study of longevity's inheritance had his reputation not been sullied by his penchant for eugenics and had he not been denounced as anti-Mendelian by Bateson. What Pearson established and legitimized was the way to study biometric traits, such as height, weight and longevity, through distributions, and he effectively invented population statistics in order to study distributions (although Francis Galton is usually given the credit). When the frequency of a biometric trait was found to have a normal, bell-shaped distribution, Pearson argued, some biological constraint determined the mean (the vertical line at the center of the bell), while small variations expressed among members of a population and the chance of the draw explained the error or scatter of points around the mean (the area beneath the bell on either side of the mean). The mean and scatter, in terms of the standard deviation of the mean, provided a basis for describing and comparing distributions, but in the early days, attempts to define the "significance" of differences was left to "good judgment."[38]

Pearson proceeded to work out a mathematics of skewness—the asymmetry of a distribution favoring one side or the other—when things got lopsided and the mean (average) and mode (most common value) did not match. Pearson proposed dissecting skewness by identifying normal curves within observed distributions. Pearson should also be credited with introducing biologists to the study of distributions, inventing variance and the standard deviation to describe scatter, and devising the chi square method for evaluating statistical differences.

Regrettably, Pearson's biometrics hardly got off the ground, and he did not establish curve analysis as a standard instrument for studying longevity. Instead, quantitative genetics replaced biometric analysis when Ronald Fisher, J. B. S. Haldane, and Sewall Wright packaged genetics and natural selection together with literary and mathematical eloquence in a new synthesis, followed by Theodosius Gregorievitch Dobzhansky's "New World" synthesis or "synthetic theory" of evolution, and Julian Huxley's "modern synthesis," launching the reign of still-fashionable neo-Darwinism. Darwinian evolution was thus rescued from the junk heap of unproven hypotheses, but at the same time, the study of heredity was directed toward (reduced to) the Morgan style of particulate genes on chromosomes and away from the Pearson style of curve analysis. The difficulty geneticists had explaining why biometric distributions were smooth rather than stepwise to meet the requirements of qualitatively discrete genes was soon rationalized as the environments' ability to burnish rough edges and as statistical error surrounding additive effects of quantitative genes.

Model Systems

Genetics has proved an overwhelming boon to the fortunes of biology. Virtually any research project stated in genetic terms will be funded by a governmental or nongovernmental agency. Thus the genetics of aging, dying, and death are widely studied in so-called model systems, namely, budding yeast, *Saccharomyces cerevisiae (S. cerevisiae)*, the roundworm, *Caenorhabditis elegans (C. elegans),* the fruit fly, *Drosophila melanogaster* (*Drosophila*)[39], and, since the advent of patented, bioengineered mice, in the laboratory mouse, *Mus musculus*.

The overwhelming advantage of working with model systems has been apparent since bio-gerontologist Raymond Pearl's classic work on fruit flies,[40] namely, model systems allow the experimenter to use laboratory reared, genetically homogeneous organisms (and throw away the organisms without pangs of conscience after performing experiments). In addition, the organisms chosen for model systems are highly fecund and have short generational times, making the study of aging that much easier and cost efficient

compared to waiting around while a slowly reproducing and slowly aging organism responds to experimental manipulation. But the experimental genetics' approach to longevity research in model systems would not have gotten to first base if it had not shown that "remarkable life-span extensions can be produced with no apparent loss of health or vitality by perturbing a small number of genes and tissues."[41] Although this quotation is borrowed from a study on the roundworm, similar conclusions are drawn from work on yeast, flies, and mice.[42] Indeed, these model systems are said to have turned up a number of "mammalian gerontic genes (those specifically associated with the aging process)."[43]

No doubt, genes can influence life expectancy or aging phenotype. Some genes or mutations expand life expectancy, if at a price by way of competitive disadvantage,[44] and some genes shorten life expectancy through a variety of mechanisms.[45] Caleb Finch testifies in favor of "inarguably, programmed senescence," citing, as his exemplar, genes determining "deficient mouthparts . . . [of insects with an] adult phase of 1 year or less."[46] For example, the ultra-short life of some adult mayflies (literally minutes to a few weeks) is correlated with the insect's genetically determined aphagous anatomy.

And mutations determining abnormal anatomies may also affect longevity. For example, in *Drosophila*, a mutant gene known as *vestigial,* which causes shriveling of wings, also causes premature death. The average life expectancy of female and male flies expressing *vestigial* is reduced 41 and 31 percent, respectively. But whether *vestigial* is a gerontic gene is another matter. Rather, *vestigial* would seem somehow to have affected anatomy and, only secondarily, the aging process.

On the theoretical side, the chief problem faced by gerontologists trying to assess the role of longevity genes in model systems is identifying genes affecting universal aging processes rather than species-typical processes. For example, as pointed out in a recent review of progeroid syndromes in human beings, "in *D. melanogaster* females, . . . a major cause of aging and death is the toxic effect of compounds present in the seminal fluid products secreted from the male fruit fly accessory gland. . . . [These compounds are] not considered a primary cause of mammalian aging. Similarly, . . . replicative senescence (the loss of divisional capacity in the mitotic tissue compartments of the soma) is not a potential aging mechanism for organisms whose soma are completely postmitotic, such as *C. elegans.*"[47] Later, the authors point out that *C. elegans* dies of extreme cuticle thickness and *S. cerevisiae* of extrachromosomal ribosomal DNA circles, neither of which mechanism would seem of universal relevance or particular importance to human beings.[48]

On the practical side, the chief problem posed by genes in model systems would seem to be specificity: that *Homo sapiens* is *Homo sapiens* and not *S. cerevisiae*, *C. elegans, D. melanogaster,* or *Mus musculus.* As demonstrated

above, the survivorship curve for *Homo sapiens* has its own species-typical shape, suggesting that *Homo sapiens* is adapted to its own, species-typical niche, which, if not unique, is undoubtedly different from the niches of the chief model-systems. Even de Grey, who asserts that "[i]t is to be expected that aging of rather distantly related organisms will share fundamental characteristics," also acknowledges that the same organisms "will fail to share more secondary characteristics—just as is in fact seen."[49]

One is not surprised that the survivorship distribution for *Drosophila* (and one might add *S. cerevisiae*) can be blown upward from virtually straight diagonal lines to complex inverted S shapes through the manipulation of environments, and one cannot doubt that selective breeding can result in both lengthening and shortening longevity in *C. elegans* by enhancing or inhibiting lethal and deleterious effects of genes. Clearly, the short-lived model systems currently under study are appropriate for their intended purpose—aiding the study of qualitative, longevity genes—and they have been eminently successful for discovering such genes. It is only the relevance of these genes to human aging, dying, and death that is questionable!

Human Studies of Longevity's Genetic Controls

Several direct approaches have been taken to determine genetic contributions to longevity in human beings. The traditional approach evaluates pedigrees and familial correlations at the age of death. For example, one would be tempted to conclude that inheritance played a large role in the case of the extraordinary longevity of Jeanne Calment, who died at 122+, since her "direct forbearers . . . lived on average 80 years compared to only 58 years for the ascendants of other members of her family of the same generation."[50] The problem with pedigree studies is translating them from mere anecdotes without quantitative prospects into serious efforts to identify genes with definitive roles in longevity. Efforts to solve this problem are traced by Raymond Pearl in *The Biology of Death* and, with his daughter, Ruth DeWitt Pearl, in *The Ancestry of the Long-Lived.*

The idea of pedigree and familial correlations is deceptively simple: if heredity plays a part in longevity, those with the greatest longevity should be the offspring of long-lived or "longevous" parents and the parents of longevous progeny. Karl Pearson and Miss Beeton (*sic*) performed the first test of this hypothesis using the technique now known as meta-analysis. Together they gleaned data from published records of the peerage, the landed gentry. These data covered the ages of fathers and sons at death and brothers dying beyond the age of twenty. Later, records from the English Society of Friends and the Friends' Provident Association were added to the analysis in order to study deaths of female relatives and infants. All these data on age at

death were paired for parents and offspring (direct lineal inheritance) and for offspring of the same parents (collateral inheritance); the coefficient of correlation—the degree of mutual dependence—was calculated for each pair, and statistical significance was assessed by comparisons to the probable error. All the correlations judged to be significant were positive, meaning that the life spans of parents and offspring increased in unison.

Alexander Graham Bell then studied the Hyde family in a similar way. Of 767 offspring who lived to eighty years or more, 48 percent had parents who lived to eighty years or more. In Pearl's words, "there is a definite and close connection between the average longevity of parents and that of their children." Pearl, then, strikes a proverbial note in summarizing Bell's finding: "[A] careful selection of one's parents in respect of longevity is the most reliable form of personal life insurance."[51]

According to Bell's data, longevous parents add as much as twenty years to the average life span of their offspring. These twenty years would correspond to the contribution of genes to longevity. Similarly, if not quite, according to a canvass of prominent physicians at the time, longevous parents would add about thirteen years to the average life span of offspring if diseases encountered in a lifetime are factored out (based on the mortality experience of 1900–1910).

But all is not well with correlation coefficients in the study of the hereditability of longevity. Indeed, rather than extreme long life running in families, "[t]he extremely longevous person tends to be exceptional, even in his own sibship."[52] Working on an extensive data set of parent-offspring correlations, Pearl and DeWitt Pearl concluded, "that the biometric method of correlation, as it has hitherto been applied to the problem of the inheritance of longevity, is an inadequate and unreliable method."[53]

The overriding problem with pedigree and familial correlation studies is that genes for normal longevity (as opposed to genes for progeria, Hutchinson-Gilford syndrome, Werner syndrome, and other congenital disorders) have never been successfully associated with either discontinuous variables, that is, qualitative (Mendelian) genes, or with continuous variables or quantitative (poly-)genes. In effect, pedigrees may not be tracing genes as such. But all is not lost: this problem is confronted (if not overcome) by twin studies, which make it possible to draw distinctions between environmental and genetic effects on heredity.

Unlike pedigree and familial studies, twin studies offer a direct approach for estimating the dimension of genes's role in longevity. The relevant variable is called "life span heritability," the proportion of variance among individuals at the age of death that is attributable to differences in genotype. Life span heritability is ascertained in twin studies by comparing the mortality rates and age at death for twin-pairs, both identical and like-gender fraternal twins, including twins reared apart, as well as brothers and sisters in the remainder of the

population. Surprisingly, a Danish twin study concluded that "longevity seems to be only moderately heritable," with a genetic component no greater than 26 percent for males and 23 percent for females.[54]A Swedish twin study found that any genetic effect was small, or even absent for males.[55] With percentages such as these—closer to 0 than 100 percent—notions of genetic control over maximum life span in human beings are hardly robust and persuasive. Indeed, the demographer Väinö Kannisto concludes, "The heritability of longevity . . . is very weak."[56]

Is Longevity Ultimately Inherited?

Whether one considers longevity inherited or not will depend on what is meant by "inherited." One will have a different answer if one interprets "inherited" to mean strictly by Mendelian genes as opposed to all the other influences—epigenetic and environmental—that impinge on heredity.

Longevity is certainly genetic, but in the special sense that genes operate against alternatives. Genes set many biometric parameters in this negative way. For example, genes determine that we are not, on average, eight feet tall and do not weigh five hundred pounds. Our species' genes resist these possibilities. But this is not to say that we possess genes that determine our average height or weight. Likewise, at present, in developed countries, half of us will live to about 80 years and not to 120 years. This is not to say that we have genes for an 80-year lifetime, but genes would seem to militate against our living to 120 years.

Beyond Mendelian genes, many biological attributes bear some relationship to the inheritance of longevity. For example, small mammals with high metabolic rates, such as mice and rats, live relatively short lives compared to large mammals with relatively low metabolic rates, such as horses, humans, and bowhead whales. But none of these parameters determine longevity any more than genes. Indeed, "*[t]here is no generally valid, orderly relationship between the average duration of life of the individuals composing a species and any other broad fact now known in their life history, or their structure, or their physiology.*"[57] Even metabolic rate gives no reliable clue to life span generally. Bats, for example, have higher metabolic rates than mice and rats but live relatively long lives. Similarly, birds with high metabolic rates live longer than mammals of comparable size and low metabolic rates. Likewise, other biometric parameters—body size, weight, brain size, brain size–body weight ratios—would seem to have a bearing on longevity in some species but not in others. Indeed, no amount of shuffling data has demonstrated an unambiguous correlation of longevity with any biological attribute.

Possibly, bio-gerontologists are looking for the wrong sort of thing in their quest to attribute longevity to heredity. Could longevity exhibit non-Mendelian inheritance? The correlation of offsprings' longevity with the male

parent's age points in that direction (see chapter 5 for further details). According to a *Sidney Morning Herald* journalist who covered a recent international longevity conference, "Research from the University of Chicago's Centre on Ageing shows that daughters born to fathers in their late 40s or older live, on average, three years less than other women, yet their brothers are not affected. . . . But the answer is not to leap into fatherhood early in life, because daughters born to fathers aged under 25 also have a shortened life span, said the center's research associate, Natalia Gavrilova."[58]

Natalia Gavrilova also looked at links between long life and motherhood: "We found that, in contrast to previous reports by other authors, women's exceptional longevity is not associated with infertility. . . . There is no relationship between childlessness and longevity."[59] Gavrilova may have taken her cue from the science-fiction writer Bob Shaw, who portrays a society of impotent immortal males but perfectly fecund immortal females.[60] Other, more fruitful, avenues for research may lie ahead, but let us lay to rest the notion of killer genes. In sum, we do not die, at least not directly, at the behest of any gene.

DO WE DIE AT THE COMMAND OF KILLER ENVIRONMENTS?

There is, of course, no end of things in our environment that can kill us, from accident to pollution and from trauma to infections. That's not the problem. The problem is that, like genes, we cannot live without our environment. Life is a compromise with both our genes and our environment. There is no such thing as perfection. We simply make do with what is at hand, although we might wonder if other environments, like other genes, might keep us alive longer and better.

Environments enter mortality statistics in two ways: causes of premature death and promoters of aging. Regrettably, experimental gerontologists working at the genetic/molecular level are prone to confuse these environmental influences, for example, when arguing that "[o]ur ability to rapidly stockpile energy during periods of abundance and to conserve energy during times of famine . . . [are] ill suited to the sedentary lifestyles and rich diets of modern society."[61] No doubt, we are exposed to lots of hazards through our interactions with our environments, and becoming a "couch potato" is dangerous to our health and should be resisted or avoided, but causes of premature death, like the proverbial Mack truck, do not necessarily promote aging. Soldiers are killed by hostile and friendly fire while waging modern war, but civilians, especially children, are killed by disease, malnutrition, and neglect, none of which qualify as promoters of aging.

So much of aging involves our interactions with our environment that the environment is inevitably one of the usual suspects determining aging, dying, and death. For example, we blame close work and the sun for presbyopia (loss of close vision), loss of accommodation, cataracts, and macular degeneration, and, more seriously, mutagenic effects.[62] We also blame loud music and jackhammers for presbycusis (loss of hearing in the high-frequency range). Moreover, strains of work lower our general level of motor activity and decrease our fine motor skills, and boredom destroys our capacity for running memory.

The strongest cases for a direct environmental influence on longevity are made by the near universality with which lowering temperature (hypothermia) in poikilotherms (cold-blooded animals) including fish, and imposing a regime of caloric restriction (CR), also known as nutritional restriction (NR) and dietary restriction (DR), in a host of organisms including homeotherms (warm-blooded animals), prolongs longevity.[63] The effects of hypothermia on longevity seem to be mediated by influences on "maturation, [and] adult metabolism,"[64] while the effects of caloric restriction are thought to lower "mortality entirely as a consequence of a lower short-term risk of death."[65] These environmental effects may work through any or all of several mechanisms: by having "a protective effect . . . on fuel use"[66] through lowered plasma levels of both glucose and insulin; by inducing hyperadrenocorticism with "an effect over the lifetime similar to that of the transient acute hyperadrenocortical response to stress . . . [serving] as a buffer, [and] keeping primary defenses such as inflammatory and immune (including autoimmune) responses in check."[67] Caloric restriction, thus, could postpone or prevent "a remarkable array of diseases and age-dependent deterioration, without causing irreversible developmental or reproductive defects."[68]

The possibility that hypothermia and caloric restriction work through the same mechanism or parallel effects on metabolism is difficult to test, since homeotherms are not good subjects for hypothermia experiments. But species of mammals exhibiting natural torpor or hibernation sustain decreased body temperatures and "live unusually long in relation to their specific metabolic rate when active,"[69] suggesting that hypothermia and caloric restriction meet on the same epigenetic pathway. In particular, hypothermia and caloric restriction would seem to be linked via stress.[70] Chronic stress is typically thought of as accelerating the onset of senescence or aging, but stress also implies pressures and tensions on metabolic regulation, reproductive control, the inhibition of cellular proliferation, and the promotion of programmed cell death—all of which are relevant to the underlying bio-molecular pathways of longevity (DNA repair, oxidative stress response, release of microbicidals, and so on). In the *C. elegans,* the molecular responses triggered by environmental stress are

even called "the transcriptional equivalent of the fountain of youth."[71] In other words, environments and biological determinants cannot be separated. We no more die at the command of our environment than we die at the command of our genes.

IS IRREPRESSIBLE ENTROPY OUR EXECUTIONER?

Do we die at thermodynamics' command? Do the laws of thermodynamics that rule the universe also rule our life span? Biologists, gerontologists, and physicians, with a reductionist physical/chemical bent, have brought life and death under the umbrella of the laws of thermodynamics, contending that life is inevitably under threat because nothing dissipating energy can escape degradation! But is this scientific argument for the certainty of death compelling? Is belief in thermodynamics any more persuasive than believe in the "immutable" laws of theologians in transcendental power or the power of species, genes, and environments to kill?

Many dedicated scientists will say that death is inescapable, because we live in a thermodynamic universe in which everything rolls down an energetic hill. According to the laws of thermodynamics, in a thermodynamic universe, nothing mechanical—including living things—can operate and remain unchanged in perpetuity or ever return to an originally pristine condition. In other words, everything that uses energy ultimately runs down, and, when living things run down completely, they return to dust—nonliving stuff.

Other gerontologists have a problem with this point of view. Indeed, Raymond Pearl concluded: "A death really due to . . . a breaking down or wearing out of all the organ systems of the body contemporaneously . . . probably never, or at least extremely rarely, happens."[72] Who is right?

Thermodynamics, the branch of mechanics concerned originally with heat's movement in steam engines—hence the "thermo-" and "-dynamics" in thermodynamics—provided the theory that mastered steam and powered the industrial revolution. But thermodynamics did not stop there. Standing on the shoulders of seventeenth century giants Boyle and Newton, with temperature, pressure, and volume to guide their study of mechanical action and work, the great eighteenth and nineteenth century physicists and engineers—Boltzmann, Carnot, Clausius, Evans, Gibbs, Joule, Kelvin, Rankine, Trevithick, and Watt—devised the laws that moved beyond steam to other forms of energy and beyond boilers and pistons to other forms of engines and machines. Ultimately, the laws of thermodynamics were perceived to rule the universe: the total amount of energy in the universe is constant, but the inaccessible (useless) part of this energy tends to increase.

The first law of thermodynamics, the conservation of energy, states that energy is neither created nor destroyed but is only transformed, for example,