Paper Reference(s)

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Edexcel GCE

Biology (Salters-Nuffield)

Advanced

Unit Test 6 Synoptic Paper

Scientific Article

June 2007

The first question in the synoptic paper will relate to the following scientific article, which you should study during your course.

You may be asked to summarise the information in the article, and explain or comment on the biology and issues within the context of the article.

The question will be worth 20 marks out of a total of 60 marks for the paper.

The article is adapted from a book called *MUTANTS – on the Form, Varieties and Errors of the Human Body* by Armand Marie Leroi.

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THE SOBER LIFE

[ON AGEING]

Huntington's disease is one of the nastier neuro-degenerative syndromes. It usually first appears as a mild psychosis and does not seem especially serious. But, as the disease progresses, the psychotic episodes increase in frequency and severity. Motor-coordination also deteriorates, a characteristic rigidity of gait and movement sets in and then, eventually, paralysis. In the disorder's final phase, which can take up to ten or twenty years to appear, the patient becomes demented and experiences neural seizures, one of which is eventually fatal. The disease is caused by dominant mutations that disable a protein used in synaptic connections of the brain's neurons. For reasons that are not fully understood, the mutant form of the protein initiates a molecular programme that gradually kills the neurons instead.

Huntington's disease has several strange features. One is the way in which its symptoms become more severe from one generation to the next. This phenomenon, called 'anticipation', arises from a peculiarity of the Huntington's gene itself and the mutations that cause the disease. The gene contains a region in which three nucleotides, CAG, are repeated over and over again. Most people have between eight and thirty-six of these repeats. Huntington's disease mutations increase the number of repeats, so disordering the structure of the protein. Several mutations of this sort cripple the protein ever further over successive generations, increasing the severity of the disease.

Another oddity of Huntington's is its frequency. It afflicts about 1 in 10,000 Europeans. This is very high – most dominant mutations that kill have frequencies of about one in a million. But Huntington's disease can persist in a family for generations. In 1872, George Huntington, a New York physician, described the disorder from families in Long Island, New York. Among their ancestors was one Jeffrey Ferris who emigrated from Leicester, England, in 1634. He almost certainly had the disease, as do many of his descendants today. In South Africa, about two hundred Huntington's patients are descended from Elsje Cloetens, the daughter of a Dutchman who arrived with Jan van Riebeeck to found the Cape Colony in 1652. A large group of Huntington's patients who live near Lake Maracaibo, Venezuela, are the descendants of a German sailor who landed there in 1860.

How can so lethal a disorder transcend the span of so many generations? In 1941 the brilliant and eccentric British geneticist J.B.S. Haldane proposed an answer. He pointed out that, unlike most genetic disorders, the symptoms of Huntington's disease usually appear in middle age. By this time most people with the defective gene have had their children – each of whom will have had a 50 per cent chance of inheriting the defective gene. Unlike most lethal dominant mutations that kill in childhood and so are never transmitted to the following generation, the Huntington's mutation hardly impairs the reproductive success of those who bear it. Middle age is almost invisible to natural selection.

Few other disorders caused by a single mutation have such devastating effects so late in life. Yet the strangeness of Huntington's disease is deceptive, for Haldane's explanation of why it is so common also explains, with a little generalisation, why we, and most other animals, age. In this chapter I will argue that ageing is a genetic disorder, or rather, it is many genetic disorders, some of which afflict us all, others of which afflict only some of us. This point of view goes against the grain of most definitions of disease. Medical tradition distinguishes between 'normal' ageing, about which nothing much is done, and 'age-related diseases', such as arteriosclerosis, cancer and osteoporosis, that consume vast amounts of national health budgets. But this distinction is an illusion, a necessary medical fiction that allows physicians to ignore a disease that affects us all but which they are impotent to cure or even ameliorate. Properly understood, ageing is precisely what it seems: a grim and universal affliction.

Impotent Selection

Ageing is the intrinsic decline of our bodies. Its most obvious manifestation is the increased rate at which we die as we grow older. An eight-year-old child in a developed country has about a 1 in 5000 chance of not seeing her next birthday; for an eighty-year-old it is about 1 in 20. Of course, it is possible to be killed by causes quite unrelated to ageing – violence, contagious disease, accidents – but their collective toll is quite small. Were it not for ageing's pervasive effects, 95 per cent of us would celebrate our centenaries; half of us would better the biblical Patriarchs by centuries and live for more than a thousand years. We could see in the fourth millennium AD.

The evolutionary explanation for why we, and most other creatures, age rests upon two ideas, both implicit in Haldane's explanation for the frequency of Huntington's disease. The first is that the ill-effects of some mutations are felt only late in life. Most obviously a mutation might cause a slow-progressing disease. The Huntington's mutation is just such a time-bomb. So is the *SOST mutation* that causes *sclerosteosis* in Afrikaaners; children are relatively unaffected but the excess bone growth kills in middle age. So are mutations in *BRCA*$_1$, the familial breast-cancer gene whose ill-effects are usually felt only by women in their thirties and forties. And so is a variant of the *APOE gene* called *ε-4* that predisposes elderly people to heart attacks and Alzheimer's.

Such examples could be multiplied, yet it must be conceded that not a great deal is known about the time-bombs with the longest fuses, those that detonate past middle age and that cause senescence. For the moment, let us simply suppose that they exist. To do so, however, is not sufficient to explain ageing. It is also necessary to understand how it is that time-bomb mutations have come to be such an inescapable part of human life. Haldane alluded to the explanation for this when he argued that the Huntington's mutation is not seen by natural selection. The same logic can be applied more generally. Imagine a dominant mutation that renders a twenty-year-old man impotent for the rest of his life. In twenty-first-century Britain at least, relatively few men have fathered children by the age of twenty, and after age twenty, the victim of such a mutation will never do so. Whatever he may accomplish in the course of the rest of his life, as far as genetic posterity is concerned he may as well never have been born. The same mutation may occur many times in many men but it will, adolescent fathers aside, never be transmitted to future generations and so will always remain rare. Imagine now another dominant mutation, one that also renders its carrier impotent, but does so only at the age of ninety. For such a man, the odds are excellent that he will be quite oblivious to his loss for the simple reason that he will be dead, having been previously claimed by cancer, a cardiac infarction, influenza, or a failure to notice the approach of the Clapham omnibus. Six feet under, the cost of Viagra is not an issue. Alive and virile he will, however, have sired any number of children, some of whom will bear the mutation, as will some of their children, and so on. Indeed, it is quite possible that the mutation will, simply by chance, spread throughout the population so that, after many generations, all men will be impotent at age ninety – essentially the case today.

This argument is just a restatement of Haldane's: that the force of natural selection against deleterious mutations declines over the course of life. But it was another British scientist, Sir Peter Medawar, who first generalised this to explain the diversity of ways in which our bodies break down while ageing. Late in life, some mutations impair our cardiovascular fitness, others our resistance to cancers or pathogens, others virility, yet others our wits. Such long-fuse mutations have afflicted us forever and, unimpeded by natural selection, they have spread and become universal.

Medawar's explanation of the ultimate causes of ageing surely has a great deal of truth to it, but it has one weakness, and that is its appeal to chance. It is easy to see why mutations that cause some grievous error in old age are not selected against, but is that absence of impediment enough to account for their spread throughout humanity? Perhaps. There are probably thousands of different mutations that have ill-effects late in life, and each of these must have occurred incalculably many times in human history. It is certainly plausible that some spread by chance particularly at times when population sizes were small.

But an appeal to chance is never satisfying; we would prefer a deterministic theory. In 1957, an American evolutionary biologist, George Williams, proposed one. He argued that the mutations that cause ageing spread not by chance but because they confer some benefit, albeit only to the young. Imagine, once again, a mutation that causes impotence at age ninety, but that also confers unusual virility at age twenty. The carrier of such a mutation might well sire more children than other men, and so the gene would spread. In the calculus of natural selection, small benefits reaped early often outweigh severe costs paid later on. Old age, in this view, is the price we pay for the lavish beauty and exuberant excess of youth.

Some geneticists have used this logic to explain why Huntington's disease is so common. They argue that women with the disorder are, in the first stages of their disease, unusually promiscuous, or feckless, or at least unusually fecund. One study has shown that women with Huntington's disease have more illegitimate children than their unaffected siblings. Perhaps, the argument goes, the disorder causes unusually high levels of gonadotropin, a hormone that influences sexual behaviour. There is little evidence to support any of this.

More generally, so little is known about the genes that cause human ageing that it is difficult to know whether Medawar's or Williams's view is the more accurate. In a way, the difference between the two theories does not matter; they may both be right, for they are similar in their causes and their consequences. Both propose that ageing is not *for* anything, but is, instead, just an epiphenomenon of evolution. It is ultimately due to the inability of natural selection to act against the mutations that cause disease in the old. Neither theory says much about the mechanical or molecular causes of ageing. They do not point to any one molecular device that we can fix and so ensure our immortality. Rather, both suggest that no such device will be found, and imply that ageing is the collective consequence of many different mutations that gradually wear down and then destroy our bodies.

Perhaps this is why, despite much effort, the mechanistic causes of ageing remain so elusive. The root of ageing's evil has been claimed, at one time or another, to lie in any one of a dozen aspects of human biology. Some have claimed that it is caused by the fermentation of bacteria in our guts; others by a slow-down in the rate at which the body's cells divide; yet others have pointed to the exhausting effects of bearing and raising children. Others again have proposed that ageing is caused by the exhaustion of some vital substance, or else that chemicals produced by our own cells gradually poison us. Many of these ideas are probably absurd, but some probably contain at least an element of truth. What follows is a survey of some of the most plausible ones: a brief history of decay.

Gerontocrats

In his declining years, flush with cash and fame from having invented the telephone, Alexander Graham Bell turned his attention to genetics. His first efforts were modest. He bred a variety of sheep with four nipples instead of the usual two. Then, combining his interests in sound and heredity, he studied the genetics of deafness. But his passion was the genetics of human longevity. He began with the family of one of America's Pilgrim Fathers, a William Hyde (settled Norwich, Connecticut, in 1660), whose descendants, all 8797 of them, had been traced by genealogists. Analysing their records, Bell concluded that longevity was mostly inherited. Neither his data nor his statistics justified this conclusion. But he wasn't far wrong – modern estimates put the heritability of European longevity between 20 and 50 per cent. In the event, it was enough to set him off on far grander plans.

Like many early-twentieth-century scientific men, Bell was an enthusiast of eugenics. Not 'negative' eugenics – the state-enforced sterilisation of the mentally disabled and the antisocial – that were vogueish in the 1920s, for this he found repugnant. Bell was a humane man; it is not for nothing that America's premier organisation for the deaf bears his name. His view of eugenics was more 'positive', liberal, indeed entrepreneurial: he saw it as an instrument in the marketplace of human affections. Bell proposed, and then began, the compilation of vast numbers of longevity records from Washington, DC, area schools. His idea was to ask children how old their parents and grandparents were, and then publish the results along with their names and addresses in a volume that he called, without equivocation, a 'human stud-book'. People, he thought, would be sure to consult his stud-book; the descendants of long-lived individuals would search each other out, fall in love, and breed. What of the descendants of short-lived people? Perhaps they would simply remain unmarried. Or perhaps long-lived and short-lived people would separate into distinct races; there would be true gerontocracy. Genetic progress, like economic progress, requires efficient markets, and efficient markets need information; it was all very clear.

Alexander Graham Bell's scheme was visionary and only slightly mad. (Who among us would choose the object of our desires on the basis of mean grandparental longevity?) Unsurprisingly, it foundered with his death in 1922. Yet had the scheme become universal, and had people behaved as Bell hoped they would, the results would surely have been spectacular. There is no doubt that the careful breeding of long-lived families would, with time, have resulted in a strain of long-lived people. Perhaps not patriarchially long-lived, but a good deal longer than the seventy-something years that is all we can reasonably hope for. We can guess this, because experimental schemes, not too different from Bell's, work in other creatures.

In the 1980s the evolutionary account of ageing given by Williams and Medawar inspired researchers to attempt the creation of a breed of long-lived fruit flies. If the ultimate cause of ageing lay in the absence of natural selection late in life, they reasoned, perhaps long-lived flies could be produced by forcing natural selection upon old flies. A fruit fly can breed at two weeks of age, almost as soon as it emerges from its pupa, but by ten weeks it is quite old, perhaps as old as an octogenarian human. Male fruit flies never survive to this age, and the few females that do, the hardy survivors, have depleted metabolic reserves, tattered wings and feeble legs.

They can, however, lay at least a few eggs. And so populations of fruit flies were bred, generation after generation, only from the eggs of the oldest flies. The effect of this was to favour genetic polymorphisms that promoted survival and fertility at old age. As these increased in frequency, the flies evolved ever-longer lifespans. The speed at which this happened was remarkable. Ten generations of selective breeding were enough to increase the average longevity by 30 per cent – in human terms the equivalent of raising life expectancy from seventy-eight to just over a hundred. Fifty generations of selection, and life expectancy doubled.

Closer examination of these long-lived fruit flies showed that they were amazingly hardy. Deprived of food or water or subjected to noxious chemicals, they survived where shorter-lived flies expired. But glory in old age exacted a cost. As the flies' longevity evolved ever upwards, fertility in early life declined. Females laid fewer eggs, males were less inclined to mate. Eschewing profligacy, long-lived fruit flies hoarded their resources and established reserves of fats and sugars instead. They became sluggards, moving, breathing and metabolising slower than normal flies.

This result was just as predicted by George Williams's theory. If ageing is the genetic price of early-life reproductive success, then, conversely, increased longevity must be bought at the cost of a vigorous and fertile youth. This implies a simple economic relationship between fertility and longevity. A fly has only so many resources; it may use them to live to an old age or it may expend them on its progeny, but it cannot do both. It's a line of argument that goes back to Aristotle. In his account of animal physiology he supposed that animals need 'moisture' to live, and that they had a limited amount of it: life is warm and wet, and death is cold and dry. 'This is why,' he writes, 'animals that copulate frequently and those abounding in seed age quickly; the seed is a residue, and further, by being lost, it produces dryness.'

Since Aristotle, numerous studies have confirmed that reproduction exacts survival costs in a variety of creatures. The severity of these costs at the limit is shown by *Antechinus stuarti*, an Australian marsupial mouse. For the males of these mice, existence is little more than sex. Their brief adult lives consist of fighting other males, wandering about in search of females and, when they find them, engaging in exhausting twelve-hour-long copulations repeated daily for nearly two weeks. Perhaps unsurprisingly, after a single mating season they are dead, their tissues showing all the signs of catastrophic senescence. By the time they are done, they are devoid of sperm, their prostate glands have shrivelled up, their testes have become invaded by connective tissue, their adrenal glands are hypertrophied, their livers necrotic, their gastric tracts are haemorrhaging, and their penises are quite flaccid.

Marsupial mice are an especially blatant illustration of the idea that ageing is the consequence of youth's excesses. But there is evidence that the same economic principle affects humans, albeit to a more modest degree. The British have, of course, no Pilgrim Fathers to genealogise. Instead they have an aristocracy, mostly dating from Norman times, whose singular, indeed defining, virtue is an obsession with their own line of descent. Traditionally, the genealogies of Britain's noble houses have been recorded in the volumes of *Burke's Peerage*, but these days a handier account of the pedigrees of most British peers, from the Dukes and Earls of Abercorn to the Barons of Willoughby de Broke, is available on CD-ROM. This database, which stretches back to 740 AD, contains, in so far as they are known, the birth dates, marriages, and progeny of the British nobility, and has been used to test the idea, evident to the parents of any newly born infant, that having children takes years off your life.

Before the Industrial Revolution, the wife of a British peer could expect to live to the age of forty-five. She could also expect to bear two or three children. These averages, however, conceal much variety in the chances of life. Some women died young, and so had very few children. Some died in the decade or two after menopause (fifty to sixty): on average they had 2.4 children. But some – albeit rather few – survived past age ninety. These elderly women had had, on average, only 1.8 children, and nearly half of them were childless.

This is a fascinating result. Not only is it consistent with the results of the fruit fly experiments, it suggests that had Alexander Graham Bell's dreams ever come to fruition, his gerontocrats would have had an ever dwindling fertility. A more sobering thought is that many, though surely not all, aspects of the senescent decline of our later years may be difficult to meliorate without damping down the physiological and sexual excesses of youth. In the future, humans may well be able to engineer themselves, be it by better drugs or better genes, to live as long as they please, but the cost may be twenty-year-olds with all the vigour, appetites and charm of the middle aged.

La Vita Sobria

Is there a recipe for long life? Luigi Cornaro thought there was. In 1550, the Venetian nobleman published a tract called *Discorsi della Vita Sobria* (Discourses on the sober life) in which he outlined the regime that had ensured his own longevity. He was probably eighty-three at the time, and lived until ninety-eight or 103 – there is some dispute about his birth date, though all agree that he reached a great age. By his own account he had, until the age of forty, lived a life of sensual dissipation. The consequences were pains in the stomach and side, gout, fever, and an unquenchable thirst. His physicians warned him that he must reform or die. He took their advice to heart and thenceforth devoted himself to a temperate and orderly way of life.

The chief ingredient of his new regime was simple: eating less, and then only what he found agreeable. 'Not to satiate oneself with food is the science of health,' he wrote. He is vague on specifics, but at the one point at which he reveals what his actual diet was, it does not sound too arduous. A typical meal would begin with bread, then a light broth, perhaps with an egg. But, he said, 'I also eat veal, kid and mutton; I eat fowls of all kinds, as well as partridges and birds like the thrush. I also partake of salt-water fish as the goldney and the like; and, among the ovarious fresh-water kinds, the pike and others.' A modest diet by sixteenth-century Italian standards then. Yet at one point he grew so thin that his friends urged him to eat more. Cornaro's oracular reply was that whosoever wished to eat long must eat little.

This is a little smug, but the *Vita Sobria* charms – Cornaro is so clearly delighted by his longevity. A portrait by Tintoretto shows him in his splendid dotage, a grave and fine-featured patrician with skin made translucent by age. Cornaro spent his last years at his Paduan palazzo with its decorations by Raphael and at his villa in the Euganean Hills by the River Brenta with its exquisite gardens and fountains. 'I did not know,' he writes, 'that the world could be so beautiful until I was old.'

The *Vita Sobria* was a huge success. As he grew older, Cornaro added material to its successive editions: two, three, and finally four *discorsi*. A product of the Italian Renaissance, the book's style was classical (Jacob Burckhardt cited it for its perfection), its physiology Aristotelian (much about moisture loss), and its sentiments Ciceronian (old age is a thing to be welcomed, a time of wisdom when passions have been burnt away). Its influence was long-lasting and can be found, for example, in the writings of the German physician Christian Hufeland, whose *Makrobiotik* (1796) outlines the theory from which every modern health-food fad ultimately derives.

The worst of it is that there is an element of truth in Cornaro's claim that the route to great longevity is eating less. By this I do not simply mean the sort of diet that will stave off gross obesity or even middle-age spread, but serious dieting of a sort that few people could sustain voluntarily. The only reliable way to extend the general physiological life of a mammal is to give it no more than two thirds of the daily calories that it wants. Dozens of studies have shown that 'caloric-restricted' mice live anywhere between 10 and 50 per cent longer than those which are allowed to eat as much as they want. Age for age, they are friskier, glossier and healthier than their controls. And they are slimmer: about half the weight of controls. Caloric-restricted mice do, of course, eventually die, but the ages at which they get diabetes, infections, renal malfunctions, autoimmune attacks, musculoskeletal degeneration, cardiomyopathy, neural degeneration and, most amazing of all, cancer are all delayed. Studies on rhesus monkeys are now under way to see if caloric restriction extends life in primates, but it will be another decade before we know the answer.

Uncertainty has not stopped many neo-Cornarists from committing themselves to lives of rigorous dieting. Caloric restriction has become a health fad like any other, with its own books and gurus. The diet usually consists of about a thousand calories per day, which is necessarily supplemented with a battery of vitamins and minerals. A thousand calories is about the minimum number needed to sustain the life of an average-sized man, though not enough to sustain his sex drive (or, to judge by pictures, his sex appeal). Whether these ultra-puritans will reap their reward is an open question. The severe caloric restriction experienced by the Dutch population during the *Hongerwinter* of 1944–45 certainly had no detectable beneficial effect on the long-term mortality rates of the survivors, but it could be argued that it takes decades of near-starvation for its virtues to become apparent.

Caloric restriction works in rats, mice, fruit flies and nematode worms. Why it does so remains mysterious. One explanation goes back to the deleterious effects of reproduction. Caloric-restricted animals have fewer offspring than those allowed to eat all they want; perhaps the energy savings that come with not reproducing are enough to ensure longevity. But there is probably more to it than this. In caloric-restricted fruit flies not only are the genes involved in reproduction largely switched off, but those involved in resistance to infection (the fly's immune system) are turned on, so that immunity proteins are produced at higher levels than they would be normally. This result suggests at least two reasons for the longevity of caloric-restricted animals. There may be many others besides. About two thousand of the fifteen thousand genes in the fly's genome show a response to caloric restriction. It is quite possible that caloric restriction works its magic by the cumulative benefits of dozens of different molecular pathways.

This should hardly come as a surprise. Evolutionary theory predicts that ageing is caused by the independent destruction of many different systems; if caloric restriction has such pervasive effects on health, then it too must work by maintaining the body in many different ways. Even so, many gerontologists still seek a single explanation for all the diverse manifestations of ageing and the way in which caloric restriction delays them. One idea is that ageing is caused by a kind of insidious poison that is a consequence of the very condition of being alive.

The Breath of Death

'We term sleep a death and yet it is waking that kills us,' observed Thomas Browne in his *Religio Medici*. That living itself is the cause of our decline – either by exhausting some vital substance or else by gradual self-poisoning – is one of the oldest ideas in the history of ageing science. In its most recent version, ageing is caused by small, pernicious molecules capable of oxidising DNA, proteins, lipids, indeed almost anything they come into contact with. In the course of normal respiration, oxygen is reduced to water. But this is an imperfect process, and several other molecular species called 'free radicals' are produced as by-products. These molecules, which have chemical formulas such as $\bullet OH$ (the • signifying an unpaired electron), are especially abundant in mitochondria, the sub-cellular structures in which respiration takes place. From there they leak into the rest of the cell, attacking other structures as they go.

The free radical theory postulates that ageing is caused by the accumulated damage that these molecules inflict upon cells over the course of years. An abundance of correlative evidence supports this. Free radicals certainly damage cells, and the kind of damage they do becomes more common in old age. Most disturbingly, they cause mutations. The DNA of each human cell receives ten thousand oxidative hits per day. While many of these are repaired, many are not. Old rats have about two million mutations per cell, about twice as many as young rats do. Most of these mutations will have no effect on the health of a given cell. But should the radical hit a gene vital for the survival of a cell it might well kill it. Should it hit a proliferation-control gene in a stem cell it might initiate a cancer. Should it hit a gene in the cells that give rise to sperm and eggs, it may be transmitted to future generations.

Free radicals are clearly pernicious. But do they cause some or all of ageing? Perhaps. Long-lived animals – be they innately so or else calorie-restricted – seem to be exceptionally resistant to toxins such as paraquat, a weed-killer that works by inducing the production of free radicals. More direct evidence comes from genetic manipulations in a variety of animals. Animal cells contain a battery of defences against free radicals, among them a group of enzymes devoted to scavenging free radicals, the superoxide dismutases. Several different kinds of evidence suggest that they protect against some of ageing's effects.

An especially active form of superoxide dismutase seems to contribute to the longevities of the fruit flies, alluded to previously, that were the result of generations of gerontocratic reproduction. The founding population of these flies was polymorphic for two varieties of superoxide dismutase. Selection changed the frequencies of these variants so that the more active form became much more common in the populations of long-lived flies than in the short-lived ones. This wasn't just a matter of chance: the experiment was replicated five times, and the same result was found each time. In an even more direct demonstration of the benefits of this enzyme, flies were engineered to express human superoxide dismutase – apparently more potent than the fly's own – in their motor neurons. They lived 40 per cent longer than un-engineered controls, a particularly interesting result, for it implies that superoxide dismutase can protect the nervous system. Finally, in the last few years many mutants have been found in nematode worms and fruits flies that seem to confer extraordinary longevity (one of them has even been named *Methuselah* after the patriarch who, Genesis assures us, lived to the age of 969). These mutants do not alter the sequences of superoxide dismutase genes themselves but rather affect genes that control when and how superoxide dismutase is activated. It is, it seems, hard to make a long-lived fly or worm without boosting superoxide dismutase by one means or another.

All these results suggest the following chain of argument: extra superoxide dismutase postpones ageing (at least in worms and flies); superoxide dismutase protects against free radicals; hence free radicals cause ageing. Does this imply that the means for postponing ageing in humans are at hand? Might we not simply engineer ourselves with a more effective superoxide dismutase and so gain years of life? The short answer seems to be no. Moreover, the reason that this won't work casts some doubt upon one of the premises of the foregoing argument.

Our genomes contain three genes that encode superoxide dismutases. Mutations in one of these, SOD_1, have been known for years. These mutations are gain-of-function and dominant: they give a hyperactive protein. It may be thought that this is precisely the sort of mutation that, by analogy with fruit flies and worms, might give a human lifespan of 120 years. In fact, they kill by the age of fifty or so. SOD_1 mutations cause amytrophic lateral sclerosis (ALS), a particularly ferocious neurological disease in which the motor neurons of the spinal cord, brain stem and motor cortex are progressively destroyed, leading to paralysis and death. In America the disorder is known as Lou Gehrig disease after the baseball player who suffered and died from it. Nowhere is the issue of physician-assisted suicide as pressing as it is in ALS.

These mutations pose a paradox. They suggest that superoxide dismutase kills motor neurons in humans, even as it protects them in flies. Why? For the last ten years this paradox has been resolved along the following lines. Superoxide dismutase is only the first step in an enzymatic pathway that neutralises free radicals. It converts the free radical oxygen anion, $O\bullet_2$, to another molecule, H_2O_2, more commonly known as hydrogen peroxide, whose destructive effects upon biological tissue can be gauged by its fame as the active ingredient in chemical drain-cleaners and the classic suicide blonde. It takes another enzyme, catalase, to neutralise hydrogen peroxide by converting it to water. Perhaps an imbalance in the activity of these two enzymes in humans, but not flies, leads to a build-up of hydrogen peroxide in neurons and kills them.

It is a reasonable explanation, but it appears to be quite wrong. The reason that SOD_1 mutations kill motor neurons has nothing to do with free radicals or hydrogen peroxide poisoning. Rather, their deleterious effects seem to be related to some other, slightly mysterious, role that superoxide dismutase has in the brain. Neurons are strange cells. They are large, have long protrusions called axons, and a whole special cellular architecture that goes with this. Besides scavenging free radicals, superoxide dismutase appears to have some role in this architecture. Biologists have adopted a lovely phrase to describe such multi-tasking proteins – they call them 'moonlighters'. Moonlighting SOD_1 may also contribute to another neurological disorder, Down's syndrome. Children with Down's syndrome have three copies of chromosome 21 – the chromosome on which the SOD_1 gene resides – instead of the usual two. Hundreds of different genes reside on this chromosome, and any or all of them might contribute to the distinctive features of Down's (mental retardation, the facial abnormalities, heart problems to name but a few), but the extra copy of SOD_1 has long been fingered as one of the more destructive.

If superoxide dismutase moonlights, then the argument proposed above is predicated on a false premise. And with it goes one of the few good reasons for believing the whole free radical theory of ageing. The proponents of this theory (and among scientists they surely number in the thousands) may well feel that this is a harsh assessment of the only mechanistic account of the origin of ageing that has any pretensions to generality. It is certainly still possible that superoxide dismutase's seemingly beneficial effects on ageing are mostly due to free radical scavenging, but this remains to be shown. For the time being, however, few would disagree that superoxide dismutase can be struck from the list of elixirs that might one day stave off the decline of our later years.

A Wrinkle

Even if free radicals are not the sole, or even major, source of mutations, mutations may still cause at least some aspects of ageing. Mutations may be especially destructive in those tissues, such as skin, whose cells divide continually throughout life. Some of us keep relatively youthful complexions well into old age, while others wrinkle when young. This variety partly depends on the exposure to the elements, sun most obviously, that each of us has received; ultraviolet light is a powerful mutagen. But even sheltered skin ages. And for all the parasols, veils and sun-block in the world, no thirty-five-year-old's skin has ever glowed as it glowed when she was fifteen.

Wrinkling is a manifestation of a deeper inability of epidermal cells to replace themselves and maintain the integrity of the connective tissue of our skins. It is a problem that pervades our bodies. This is evident from people whose skins and connective tissues age with unusual, indeed catastrophic, rapidity. An inherited disorder called Werner's syndrome causes its victims to go grey and bald when still in their teens. In their twenties, the testicles atrophy in men as the ovarian follicles do in women – a kind of premature menopause. In their thirties sufferers need lens transplants to cure cataracts, and their arteries stiffen and become covered in fat deposits. In their forties they die, usually from heart attacks.

Werner's syndrome is one of a group of inherited rapid-ageing disorders called 'progerias'. The disorder is caused by mutations that disable a protein that maintains the integrity of DNA during replication. Cells that lack the protein have very high mutation rates. This barrage of mutations causes the cells to die instead of proliferating, or else to produce abnormal proteins. Tissues, such as skin, which rely on large numbers of dividing cells in order to maintain their integrity, fall apart. Perhaps something similar happens to us all, only at a much slower rate.

As we age, vitality slips away from our cells. This can be seen in the laboratory. It has long been possible to grow human cells in petri-dishes by means of elaborate and delicate protocols. No matter how salubrious their environment, however, freshly harvested cells will divide only a certain number of times and then divide no more. Their decline is gradual, and is caused by some intrinsic limit. Many have suggested that this cellular senescence is not merely a consequence of the ageing body but its direct cause.

Supporting this idea, cells taken from human foetuses can divide for about twice as many generations as can those from ninety-year-olds before sinking into decline. Perhaps, then, elderly people have many cells that are closer to the end of their replicative lifespans and which are, therefore, unable to contribute to repairing the wear and tear of everyday life as well as they might. When, therefore, in 1998, the molecular cause of the limit to cell division was discovered, and then broken, the thrill was tangible. If cellular senescence could be cured, perhaps so could ageing.

Each time a cell divides, its chromosomes must be replicated as well. But the enzymes that replicate chromosomal DNA are unable to replicate the ends of the chromosomes. These ends are, therefore, protected by sequences, thousands of base-pairs long, called telomeres that are gradually whittled away over the course of many cell divisions at a rate of about a hundred base-pairs per cell division. When the telomeres are gone, the cell can no longer divide and it dies. It is the rate of whittling that sets the fundamental clock of ageing. Or so the argument goes.

What is needed, then, is a way to prevent the attrition of telomeres. Not all cells lose their telomeres. The germ cells that give rise to eggs and sperm possess a complex enzyme called telomerase that maintains their telomeres and so confers upon them the immortality that they must necessarily have. The loss of telomeres that occurs in the rest of the body's cells is precisely due to the fact that they do not contain this enzyme. If telomerase is engineered into cells that normally lack the enzyme, their telomeres are preserved division after division. The cells also become immortal.

If the route to cellular immortality is so easy, why have we not taken it? The reason is quite simple: immortality is a property of cancers. Nearly all tumor cells have, somewhere in their history, undergone mutations that cause them to have telomerase where other cells do not. The absence of telomerase in our cells is probably one of the first defences we have against the multiplication of rogue cells. Besides, there is still little to show that short telomeres do, in fact, cause ageing. Only one experiment has addressed the problem directly: an experiment in which telomerase-defective mice were engineered and then bred for six generations.

Mice, it seems, can get by without telomerase for at least a while. The first generation of telomerase-defective mice that was ever produced showed no signs of premature ageing. In a way this is not surprising. These mice had telomeres as long as those of any other mice, for mice, like us, inherit their telomeres from their parents, and their parents were normal. For want of telomerase in their germ cells, however, each successive generation of these mutant mice started life with even shorter telomeres. The effects became apparent by the fourth generation when the male mice proved to have few viable sperm. By the sixth generation they had none at all. Females were not sterile, but they produced fewer eggs than normal, and those they did produce often gave rise to defective embryos. By the sixth generation, too, male and female mice alike began to age prematurely. Like humans, mice go bald and grey with age, and the sixth-generation mice did so while still young.

These results provide at best mixed support for the idea that a want of telomeres causes ageing. Sufficiently short telomeres can clearly cause premature ageing; but since this happens only after six generations of attrition, they cannot be the cause of normal ageing in mice. While it is tempting to dismiss the whittling away of telomeres as an explanation of ageing in humans, it is probably too soon to do so. Laboratory mice have extraordinarily long telomeres – far longer than ours. If our telomeres are rather short at the start of our lives and must, by virtue of our greater size and longevity, undergo far more attrition than a mouse's, it remains quite possible that they matter to us.

One way to prove the point would be to clone a human. Clones should start life with abnormally short telomeres, for they are produced without the aid of germ cells and so their telomeres are never renewed. Successive generations of clones should have shorter and shorter telomeres and age with increasing rapidity – all the more so if the clone-donors are elderly. What with the global ban on human cloning this experiment is not likely to be carried out soon – unless by UFO cultists or renegade Italian obstetricians. But, of course, it has been done in animals. Sheep 6LL3, a.k.a. 'Dolly', got her chromosomes from the udder-cells of a six-year-old Finn Dorset. She therefore began life with substantially worn-down telomeres. Many thought that she would age fast. Some arthritis aside, however, she was quite healthy; there was nothing exotic about the viral disease that prompted her euthanasia at the age of six. Clones of other animals such as cattle and mice often suffer from a variety of health problems such as obesity, but none have been reported to be progeric. Still, these are early days.

Telomerase-mutant humans would be informative too. There is another progeria, rarer than Werner's but even more severe, in which catastrophic ageing begins in childhood. The victims of this disorder usually die by the age of twelve or so, again from heart attacks, by which time they are to all appearances very small octogenarians. Their symptoms suggest defective telomeres. Even if this grim disease can be explained by too-rapid cellular senescence, we will have penetrated only a small way into ageing's mysteries. For while the progerias hasten some aspects of physical decline, they leave the minds of their victims untouched.

Making a Century

In the last ten years there has been a revolution in the study of ageing. Much of it has come from the study of the nematode worm *Caenorhabditis elegans*. This worm is only about 1 millimetre long, and it is possible to grow thousands of them in petri-dishes. They are perfectly transparent. Under a powerful microscope it is possible to see every single one of the 959 cells in their living bodies. For whatever reason, it has been especially easy to identify worm mutants that are extraordinarily long-lived. Some of these mutant worms live twice as long as normal worms do: forty-two days – in human terms, about 150 years.

So far, at least a hundred genes have been identified in worms that, when mutated, cause them to live longer. Many of these mutations disable the worm's insulin-like growth-factor-signalling pathway. As a consequence of doing so, the whole physiology of the worm changes. Mutant worms that are defective for IGF signalling reproduce less, store large amounts of fat and sugars, and activate a whole battery of genes that encode for stress-resistance proteins, among them superoxide dismutase. The result is worms that radiate health even as their normal contemporaries whither in their petri-dishes.

We have come across insulin-like growth factor before. It is the lack of this hormone that makes pygmies small and its excess that makes great danes large. It is also one of the hormones that, when inactivated in mice, cause them to be dwarf and long-lived. In worms, IGF does not seem to control body size (something of a surprise since it does so in so many other creatures, including fruit flies). Even so, taking these findings from worms together with what is known about IGF in mice, flies and many other creatures, it is possible to sketch an account of a mechanism, perhaps universal to all animal life, that allows animals to live longer when they need to.

Worms are not frightfully bright. The nervous system of any one worm, including what passes for its brain, contains only 302 neurons; a human brain has around a billion-fold more. Even so, a worm has nous enough to know how much food it has. When a worm perceives that it is about to starve, neuronal signals from sense organs in its head signal the rest of the body and IGF signalling is shut off. A change in environment mimics what many mutants do, and the result is the same: the worm lives longer.

This should sound familiar. It is, in effect, what happens in caloric restriction in mice and rats. And it suggests an interpretation for how and why *la vita sobria* has its beneficial effects. Far from being an odd laboratory phenomenon of interest only to gerontologists and diet gurus pursuing dreams of immortality, the caloric restriction response is probably a device that has evolved to allow animals to cope with the vicissitudes of life. Perceiving that it is in for hard times, a young animal alters its mode of life. Instead of investing resources in growing large and reproducing soon, it switches to survival mode. It remains small and ceases to reproduce, in effect gambling that sooner or later better times will come. If this view of caloric restriction is correct, then its enthusiasts are attempting nothing less than the revival of devices evolved to cope with the deprivation that was surely our lot for millennia of prehistory (and surely a lot of history too). Though they do not know it, when they calculate their foods to the last calorie, surround themselves with bottled vitamins, and monitor, as they must, their bone density by the month, they are playing the part of civilisation's most dedicated discontents.

Can longevity genes be found in humans? Many scientists think so. In France, Britain, Holland, Japan, Finland and the United States gerontologists are busily compiling lists of centenarians and analysing their DNA in order to find out why they live so long. They do so not in the expectation that there is any one mutation or polymorphism that all these centenarians have in common – and they fully accept that some centenarians will have made their century by a combination of good luck and virtuous living. Rather, the approach is to scan many genes which, for one reason or another, are believed to contribute to the diseases of old age and to search for those variants that are more common in geriatric survivors relative to the rest of the population.

One of the first longevity genes to be identified in this way was apolipoprotein E (APOE). The protein encoded by this gene comes in several polymorphic variants called ε2, ε3 and ε4. About 11 per cent of Frenchmen and women under the age of seventy carry at least one copy of the ε4 variant, but in French centenarians this number drops to 5 per cent, the difference being made up by the ε2 variant, which becomes more common. This implies that should you wish to see your hundredth birthday, you should hope to have at least one copy of ε2 but none of ε4.

This is because the APOE gene, which encodes a protein involved in cholesterol transport, has been implicated in Alzheimer's disease. About one in ten people aged sixty-five or over will contract Alzheimer's, but the odds are skewed drastically if you are an ε4 carrier. One copy of ε4 relative to none increases your risk of Alzheimer's three-fold; two copies increases your risk eight-fold. Were this not enough, ε4 also predisposes to cardiovascular disease. With this sort of molecular double jeopardy it is easy to see why ε4 carriers rarely survive to a great age.

All this seems to matter less if you are black. Surveys of APOE genes have shown that ε4 is very common in sub-Saharan Africa. Nearly half of African pygmies carry at least one copy. Does this really mean that Alzheimer's disease is rampant among the Efe? The short answer is that we don't know. No studies on the epidemiology of Alzheimer's seem to have been carried out on pygmies, and they would be hard to do since a high rate of death due to infection and accidents means that few pygmies survive to an age when Alzheimer's might be seen. This, in itself, may explain why ε4 is so common among them, but a more likely explanation is that it is less dangerous to Africans than it is to Europeans. Several studies have sought, and failed, to find an increased risk of Alzheimer's in Nigerians and African Americans who carry the ε4 variant. Why this should be so is something of a mystery.

In Europeans, at least, the genetics of Alzheimer's provide a beautiful illustration of the evolutionary theory of ageing that is, if anything, even more persuasive than that of Huntington's. Even among the clearly susceptible (white) French, ε4 is common for such a lethal variant, and its presence can only be explained by the fact that it has little net effect on the reproductive success of its carriers. The contrast with other genes that cause Alzheimer's is instructive. Mutations in at least three other genes cause Alzheimer's but do so at around age thirty. They kill their carriers in their prime and, exposed to the full force of natural selection, are accordingly – thankfully – rare.

These kinds of findings are only the beginning. Within a few years, dozens, if not hundreds, of polymorphisms will be found that add years to our lives or else take them away. Most of these polymorphisms will either hasten or else delay the features of ageing with which we are familiar: senile dementia, arteriosclerosis, kidney failure, prostate failure, menopause, cancer and the like. No single person's genome will possess all the variants that might be desirable for long life. This much is already apparent from the sheer diversity of ways in which we die. But it will be possible to describe in actuarial terms the relative risk of possessing a given genome. Here is a taste of what is to come. All else being equal, a forty-year-old whose genome has the following variants:

SRY(–/–); APOE(ε2/ε2); ACE(D/D); MTHFR(Ala222/Ala222)

will have a lower risk of cardiovascular disease, and hence a lower yearly risk of death, than someone with the following:

SRY(+/–); APOE(ε4/ε4); ACE(I/I); MTHFR(Val222/Val222).

The difference between these two lists is quite unmysterious. These are four genes – SRY, APOE, ACE and MTHFR – each of which has two variants known to be associated with a difference in the mortality rates of middle-aged or elderly people. These two lists are, then, a predictive theory of longevity, but one that is no more profound than the assertion that someone who neither smokes, drinks, drives or has sex will generally live longer than someone who does all those things. Only here the risk factors lie in the genome.

Possession of the second genome does not inevitably spell an early death. While it is not possible to diet your way out of Alzheimer's, much can be done to prevent a heart attack. That these genes confer different risks of death at any given age seems certain, but it is not yet possible to translate those differences into years. To do so requires large population studies of a sort that have not yet been done, but that surely will. There is one exception to this. In the USA, SRY(–/–) individuals live, on average, five years longer than those who are SRY(+/–). This, of course, is rather hard on those of us who are SRY(+/–), but there's not a lot that can be done about it except to give a Gallic shrug and mutter *Vive la différence*.

Ever Upwards

In 1994 a remarkable thing happened. Not a single eight-year-old Swedish girl died. Not one succumbed to the 'flu; not one was hit by a bus. At the beginning of the year there were 112,521 of them. At the end of the year they were all still there.

It was, of course, a statistical fluke. In that same year some eight-year-old Swedish boys died, so did some seven- and nine-year-old girls, and a few eight-year-olds of both sexes died the following year. But the survival, in that year, of those Swedish girls may be taken as symbolic of the greatest accomplishment of industrial civilisation: the protection of children from death.

Childhood mortality rates in the most advanced economies have become vanishingly small, particularly when death due to accident or violence is excluded. It is this accomplishment, at least 250 years in the making, which has driven the long climb in human life expectancy. Before 1750, a newborn child could expect to live to twenty years of age; today in the wealthiest countries a newborn can expect to live to about seventy-five. Most of this increase can be credited to the elimination of infectious diseases that preferentially strike the young. The curious thing, however, is that even though the protection of the young is largely a completed project – in the wealthiest countries – life expectancy continues to rise.

The 1960s were, it is said, revolutionary. But far from the *Sturm und Drang* of the cultural and sexual revolutions, something far more important was happening. Mortality rates of the old began to decline. An American woman who turned eighty in 1970 had a 30 per cent chance of surviving another decade; had she turned eighty in 1997 her chance of doing so would have increased to 40 per cent. The same phenomenon can be seen in the progress of maximum longevity in Sweden. Between 1860 and 1960, the age at death of Sweden's oldest person increased steadily, decade by decade, at a rate of about 0.4 years. Between 1969 and 1999, the rate of increase climbed to about 1.1 years per decade. We have been living longer for some time, but since the 1960s we have been living longer ever faster.

These numbers tell us that not only can ageing be cured, but that cures have been coming thick and fast. If ageing is the age-dependent increase in the mortality rate, then anything that ameliorates the mortality rate is, by definition, its cure. The decline of mortality rates among the old is mainly due to a several-decades-long decline in cardiovascular disease and cancer. Cardiovascular disease has been the leading cause of death in the United States since the 1920s, but between 1950 and 1996 its contribution to the death rate declined by half. In Japan, cancer rates began to decline in the1960s; in the rest of the industrialised world the decline began about twenty years later. Nothing spectacular, then, just the incremental advance of public health.

But incremental advance is all we can reasonably expect. Evolutionary theory and the increasing flow of information about the genetics of ageing, be it premature or postponed, tell us that ageing is many diseases that will have to be cured one by one. At the same time, there is no obvious impediment to that advance; nothing to make us think that human beings have a fixed lifespan. In 1994, 1674 eighty-year-old Swedish women died. It is impossible to predict what medical breakthroughs will be required to ensure that none will die in the future. But when that day comes, it will mark the completion of industrial civilisation's second great project: the protection of the old from death.

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