

Oxygen

The Molecule that made the World

Chapter 14: Beyond Genes and Destiny

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About

Dr Nick Lane is a British biochemist and writer. He was awarded the first Provost's Venture Research Prize in the Department of Genetics, Evolution and Environment at **University College London**, where he is now a Reader in Evolutionary Biochemistry. Dr Lane's research deals with evolutionary biochemistry and bioenergetics, focusing on the origin of life and the evolution of complex cells. Dr Lane was a founding member of the UCL Consortium for Mitochondrial Research, and is leading the UCL Research Frontiers Origins of Life programme. He was awarded the 2011 BMC Research Award for Genetics, Genomics, Bioinformatics and Evolution, and the 2015 Biochemical Society Award for his sustained and diverse contribution to the molecular life sciences and the public understanding of science.



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OEDIPUS KILLS HIS FATHER AND SLEEPS WITH HIS MOTHER. He does all this in ignorance: he had been left for dead at birth and raised in another land. He returns unknowingly to his homeland and becomes a good and noble King, only to be cut down by the machinations of fate. His terrible future is revealed by the blind sage Tiresias: “Blind from having sight and beggared from high fortune, with a staff in stranger lands he shall feel forth his way; Shown living with the children of his loins, their brother and their sire, and to the womb that bare him, husband-son, and, to his father, parricide and corrival.”

When I first read Sophocles' great tragedy, I was amazed at how un-Freudian the story was. When he discovers the true nature of his actions, Oedipus tears out his eyes and condemns himself to a wandering exile, thus fulfilling the prophecy; hardly the action of one who desires his own mother. Curiously, his wife-mother, Jocasta, is more ambiguous. She is the first to grasp what has happened, and she tries to prevent the truth from emerging. Only when she sees that Oedipus is set on the truth does she damn him and hang herself. One wonders if she would have continued as before, had the truth not been revealed; but if Sophocles intended a subplot here, he paid little attention to it. The most striking element of King Oedipus, and indeed so much of Greek tragedy, is the implacable role of Fate. The characters, for all their eloquence, are just puppets. Motive scarcely matters. Jocasta's attempt to turn a blind eye to the workings of fate merely illustrates the impossibility of her task, and the penalty for anyone who tries.

Today, millions of people enjoy reading astrology columns in daily newspapers, and some no doubt believe them, but the sense of ineluctable fate went out with Christianity.

When Adam and Eve ate of the apple of knowledge, humanity was freed to suffer or prosper of their own free will. Sin is a foundation of Christianity, yet must have been alien to the Greeks – how can Oedipus be said to have sinned, he who was condemned by an oracle before his own birth? For Christians, sin is a choice, and we are judged on the choices we make. The difference is clear in tragedy. The Greek sense of tragedy is quite unlike Shakespeare. Hamlet is faced with choices throughout the play, notably the ultimate question, “To be or not to be?” The terrible final scene is the outcome of a series of contingencies. The tragedy of Hamlet lies in the fact that it could all have been averted. One can imagine a satirical reworking, in which a peace broker brings the two sides together to mediate a solution. The mediator would have failed with Oedipus. Indeed, there was a mediator, Jocasta, and she did fail. What a tragic breed we are! The tragedy of Oedipus lies in its inevitability, the tragedy of Hamlet in its evitability. After two millennia of Christian choices, it is the inevitability of Greek tragedy that shocks us today.

For the first time since the Ancients, a sense of implacable fate is returning. The certainties of Greek theatre have been superseded by the certainties of modern genetics, which at times seem just as disturbing. We read about genes ‘for’ heart disease, cancer or Alzheimer’s disease. Few people, even the scientists working on them, have a clear idea of exactly what these genes do, but we eye them with mistrust. We resist the intrusion of insurance companies who wish to pry into our genetic makeup – to read our oracles – yet our resistance owes more to a sense of personal infringement than a questioning of the veracity of genetics. We seem to accept that if we have the gene ‘for’ multiple sclerosis, then we will go on to develop the disease. We accept the inevitability of genetics in the same way that the Greeks accepted the inevitability of Fate. The analogy is heightened by our powerlessness to alter the course of many diseases. Many people prefer not to know what they cannot change. Tiresias put it well 2,500 years ago: “Ah! How terrible is knowledge to the man whom knowledge profits not.”

MANY WRITERS HAVE RILED AGAINST the idea of genes ‘for’ diseases. No gene is ‘for’ a disease any more than an aeroplane is ‘for’ crashing. Genes, however, like aeroplanes, do go wrong. Historically, the attitude of medicine has been that this is a

mischance, a part of the human lot. The human body is tremendously complex, so there are a tremendous number of ways in which it can go wrong. Genes are one of these ways. A gene goes 'wrong' and the result is havoc. Cancer is the classic example. A handful of chance mutations lead to that most terrible of human fates. These mutations only need to happen in one cell out of ten trillion. There is no 'reason', beyond such unsatisfying explanations as mischance, environmental toxicity or genetic susceptibility.

The spirit guiding the human genome project is the apotheosis of this view: genes go wrong and cause disease. Therefore, to cure the disease, find the gene and put it right. Today this might not be possible, but in the future we will no doubt perfect gene therapy. All we need to do is excise the faulty gene and replace it with a nice new one: replace the carburettor and the engine will work again. Many single-gene disorders, such as haemophilia or muscular dystrophy, are in principle amenable to this approach. In the case of haemophilia, the gene that codes for a blood-clotting protein, factor VIII, is mutated, so the protein is absent. The protein can be replaced by transfusion, or ultimately the gene can be fixed by gene therapy. There are many practical obstacles to overcome, but in conceptual terms the only subtlety is to ensure that the right amount of Factor VIII is present at the right time.

The trouble is that single-gene disorders are rare. For the vast majority of diseases, especially the diseases of old age, a whole assortment of genes increase our susceptibility to disease. There is typically no genetic 'defect' as such. The world is too black and white – there are as many shades of grey between a working gene and a broken gene as there are between good and evil. Consider: a gene codes for a protein. If the sequence of the gene changes in the course of evolution, the structure of the protein changes. Sometimes the new protein may not work at all – in which case, if it is important, it will be eliminated by natural selection along with its bearer. Sometimes the change will have no effect on the function of the protein: it will simply be slightly different by pure chance. Then there may be several other versions that work to one degree or another. Given a particular set of environmental conditions, one of these may work best

– but that is not to say that the others are ‘broken’. Change the conditions and a different form may well work better. In the same way, a land rover is not really cut out as a city car, but comes into its own in the countryside. If you move with your land rover from the countryside to the city, and cannot afford to buy a new car, you may not be as well-adapted as before, but you are still better off than if you had to walk. The land rover is not broken.

The different working versions of a gene are known as polymorphic alleles. It is hard to over-state their importance: they are the molecular units of variation and adaptation, the very essence of the individual. The genetic differences between people do not lie in different genes but in ever-so-slightly different versions of the same genes. On average, our DNA has between one and ten variant letters in every thousand, which are known as single nucleotide polymorphisms, or SNPs (pronounced ‘snips’). These are being catalogued exhaustively, although we have a long way to go: there are expected to be a million SNPs in the human genome. When they are shuffled and recombined in sex, these SNPs account for our endless genetic variety. For exactly the same reasons, they also influence our susceptibility to both diseases and treatments.

Some polymorphic genes – particular SNP configurations – may come to predominate within a population as a result of evolutionary selective pressures. Selective pressures can blur the distinction between a pathological process and an evolutionary trade-off. Our genes must make the best of a bad job. In previous chapters, we have noted several examples of diseases that are not really pathological. Insulin-resistance in diabetes, for instance, is a genetic response to hard times, selected for over many generations. It is only pathological if a high-energy western diet is superimposed over a ‘thrifty’ genotype. Similarly, sickle-cell anaemia and the thalassaemias protect against malaria through small changes in the structure of haemoglobin. These anaemias are maintained at a high frequency in areas where malaria is endemic because the carriers do not suffer from anaemia, but are protected against malaria. How many other human diseases are maintained in the gene pool because they offer a hidden benefit is anybody’s guess.

We are left with a curious situation, in which our genes are held responsible for disease, even though there is nothing actually wrong with them. They are simply variable. To treat a disease on the basis of genetic polymorphism is to say that all individuals are different and should be treated as such. This is very close to what leading figures in the pharmaceutical industry are actually saying. There is a revolution in healthcare, we are told by commentators as distinguished as Sir Richard Sykes, the ex-chairman of Glaxo Wellcome. We are misguided if we think there is such thing as Alzheimer's disease: in reality it is a kaleidoscope of deceptive conditions, a hall of mirrors, caused by unique combinations of polymorphic genes. These combinations produce a spectrum of diseases that 'look' superficially similar – they look like Alzheimer's disease – but are in fact quite different, and may respond differently to treatment. This, we are told, is why we have had so little success in curing the disease: we dilute successful responses with less successful responses, in people whose genes were inappropriate for that particular treatment. We used to search for particular genes that predisposed us to disease, now we must consider whole genotypes. Treatments will become ever more specialised as we understand and begin to target individual genotypes. Blockbuster drugs will give way to genetic therapies tailored to individuals.

This is the rising field of pharmacogenomics and woe betide anyone who says it is misguided. It is, though. Particular genes, or even whole genotypes, may predispose us to the common diseases of old age, but in a wider sense this is irrelevant. Imagine you are crossing a road. You have a chance of being knocked over and killed. Your behaviour influences your chance of survival: if you step out into a busy road, without pausing to look, you have a far better chance of dying than if you wait patiently at a zebra crossing for the traffic to stop. We can whittle away at the statistics of deaths on the roads by introducing speed limits, sleeping policemen and better road markings, or by building bridges and subways, or by educating the public, or by clamping down on drink driving. If all these small changes were controlled by genes, then targeting each gene would have a small but incremental effect on the number of traffic accidents. However, we would only have a significant impact on mortality if we targeted all the 'genes' simultaneously; and even then we could be sure there would still be people

killed. Ultimately, the only way to prevent traffic accidents altogether is to ban cars, impractical as this may be. Similarly, in the case of diseases, we can fiddle with predisposing genes, and change our risk profile slightly, but in the end the only way of preventing the diseases of old age is to prevent old age. Is this aim as ludicrous as banning cars, or can it be done?

With this question, we return to the link between ageing and age-related disease. We saw in the last chapter that there almost certainly is a process of ageing, which is independent of age-related disease: mitochondrial respiration undermines the integrity of cells and organs regardless of whether we suffer a disease or not. We saw that mitochondrial respiration may set an upper limit on our lifespan of perhaps 115 to 120 years; but what about the reverse case? If ageing is independent of age-related diseases, are these diseases necessarily independent of ageing? In other words, would we suffer from dementia or heart disease if we did not age? Is there something inherent about being old that increases our risk of disease? The idea sounds intuitively reasonable, but the implications are far-reaching. Banish ageing and we banish many diseases.

IF OUR RISK OF DISEASE INCREASES WITH OUR AGE, then the question we should ask is not why does a particular variant of a gene predispose us to Alzheimer's disease, but why are its effects delayed until old age? This question is rarely addressed in medicine, which must try to cure people who are already riddled with specific ailments, but has been answered by the evolutionists. As we get older, our risk of accidental death accumulates, so there is less evolutionary pressure to maintain physiological function in an older person than in a younger person. Thus natural selection cannot eliminate a gene that causes Alzheimer's disease at 140, because none of us lives to that age. Selection pressure has fallen to zero. The consensus is that age-related diseases are caused by the detrimental late effects of genes that are maintained in the gene pool because their late effects are counterbalanced by beneficial effects earlier in life. There is a tradeoff between early advantages and late disadvantages. This is the idea of antagonistic pleiotropy, which we met in Chapter 12. We parked the idea there, noting

that it was not a good explanation of ageing (because it could not account for the swift and flexible changes in lifespan observed in nature) but that it was a good explanation of age-related diseases.

A common view of antagonistic pleiotropy is that our genes are out of step with our lifestyle. We spent half a million years evolving as hunter-gatherers. Restless wandering was combined with an ability to subsist on a meagre diet for weeks or months at a time. Then, a few thousand years ago, we became farmers. Food was plentiful, but the staple diets courted malnutrition. Rice, for instance, is a good source of carbohydrates and some proteins, but a poor source of other proteins and a number of vitamins. Health deteriorated. Skeletal remains show that the first farmers were less healthy than their hunter-gatherer forebears. Even so, the sheer quantity of food could support much larger populations. People lived together in towns and cities. Contagious diseases became rife. Entire cities were wiped out by plagues. For the next few thousand years, infections became the strongest selection pressure on the human genome. The genotypes of peoples living across whole continents were shaped by diseases like malaria. The high incidence of sickle cell anaemia in Africa and Asia is a direct result. Perhaps fewer people starved in the age of farming, but many died young from infections instead.

In the last few hundred years, all this has begun to change. Better hygiene, better nutrition and advances in medicine have created a brave new world, in which most of us can expect to live out our three score years and ten and more. Two hundred years is just ten generations – presumably too short to adapt to our cushy new lives. We sit around and overeat. Our genes adapted to meagreness for half a million years, and infection for a few thousand, but are caught reeling by this new onslaught. We are genetically geared to extract as much as possible from an impoverished environment, and have been transplanted into the midst of riches. In our youth, we have no problem. As we age, the abuse catches up with us. The theory of antagonistic pleiotropy says this is too bad: selection pressure is low once we are past 40 or 50. Until conditions like obesity begin to shape the reproductive population, there is next to no selective pressure for change.

Thus, our genes condemn us to rot in a world of plenty. What a depressing scenario.

There is more than a grain of truth in this pessimistic view of disease, but also some problems with it. For a start, age-related diseases have always been with us, among the lucky few who survived to old age: they did not just appear in the last couple of centuries or even millennia. More importantly, they are also found in ageing animals – and not just in captive animals, which might be overfed, but also in wild animals shielded from predation. Old mice suffer from the same sort of ailments as old people. Their joints stiffen, their skin wrinkles, they lose their ability to remember and learn, their immune system degenerates, and they have a rising incidence of heart disease and cancer. If we take a single parameter, such as the number of cross-links between collagen fibres in the skin (which cause wrinkles) there is little difference between old mice and old men. In each respect, the way that we age is strikingly similar. The difference lies in the rate. Mice and rats pass through the sequence of age-related changes in four years, we take 70 [FIG]. Similar patterns apply to other animals: the spectrum of age-related changes is similar but the rate of ageing is different. Tiny nematode worms live just a few weeks, yet still age in a way that we can recognise – they move and feed more slowly, they become infertile, their outer cuticle becomes wrinkled, and they accumulate the fluorescent age pigment lipofuscin, just as we do in our neurones and muscle cells. At the other extreme, many birds, some of which live for well over a hundred years, suffer analogous degenerative conditions to mammals, including stiffening joints, congestive heart failure, atherosclerosis, cataracts and a variety of cancers. The entire animal world cannot be out of step with its environment! There must be more to age-related disease than just a mismatch between genes and environment.

We do not have to be out of step with our environment, of course, to suffer from the effects of antagonistic pleiotropy. In Chapter 12, we noted that genetic conditions like Huntington's disease are examples of pleiotropy in action: a barely measurable increase in fecundity in youth is enough to offset the most dreadful stripping away of faculties later in life. Diet is irrelevant: the effect is written in a single gene. If we carry the gene for Huntington's disease, we will get the disease whatever we eat. Something similar may

be true of other diseases. Some polymorphic genes, such as the ApoE4 allele, increase our susceptibility to Alzheimer's disease. A quarter of the population inherits a single copy of the ApoE4 gene, increasing the risk of dementia fourfold. Two per cent of the population inherits a double dose, increasing the risk of dementia eightfold. For a gene to be this frequent in the population, we may suspect a hidden benefit earlier in life. What this putative benefit might be in the case of ApoE4 is unknown. The point is that the extra risk of dementia is not enough to rid us of the ApoE4 allele. One may well wonder how many other diseases of old age, almost all of which have a genetic component, are similar to Alzheimer's disease in this respect.

But wait a moment. Earlier in this chapter I made a strong assertion: targeting susceptibility genes is not the way to cure Alzheimer's disease, or any other age-related disease. Instead, we must try to slow the whole ageing process. The secret to this lies in the theory of antagonistic pleiotropy. The idea of antagonistic pleiotropy sounds simple enough, but there is a quandary at its heart: when is a late effect? At what point in our lives do genes start to have a negative effect, instead of a positive effect? Should we measure this 'time to negative effect' in years, or in some other kind of unit? If the units are years, then the effect of antagonistic pleiotropy is as defined as the fate of Oedipus. If we have two copies of the ApoE4 gene, we shall succumb to dementia at the hour of our appointed fate, and have little more chance of stopping it than we do of stopping time. But if the effects are dependent on age, not on time, then the tragedy of Alzheimer's disease is contingent on being old, on having crossed an age threshold, rather than the time that elapsed before we reached the threshold. Like Hamlet, our fate is then a matter of historical contingency, of having crossed the threshold, not an Oedipal certainty.

In the case of Alzheimer's disease, an age threshold may account for the wide variation seen in the age of onset. ApoE4 shifts the risk of Alzheimer's disease to a younger age, so that people with two ApoE4 genes are more likely to succumb to Alzheimer's disease by the age of 65. Yet having two copies of ApoE4 does not exacerbate the severity of dementia, or noticeably change its pathology, or speed up the clinical course. The

disease is similar in every respect, except that it happens earlier. In this sense, ApoE4 does not 'cause' the disease so much as shift a condition that would happen anyway into an earlier time frame. This implies that there is a threshold: the disease develops in the same way once the threshold has been crossed, regardless of which ApoE allele you have. The chronological age at which the threshold is crossed may vary between 60 and 140. As Einstein said, time is relative; but in the case of ageing, relative to what?

We all know some people who have aged well, and others who have aged badly. There may be a discrepancy between our biological age and our chronological age. The average life expectancy of 75 years conceals a huge amount of variation. It is not uncommon for people in their 50s to die of an age-related disease, such as a heart attack or cancer, nor is it uncommon to die over 100. It is questionable whether age in years is as useful an indicator of life expectancy as biological age. There are numerous ways of thinking about biological age, but a reliable way of quantifying it is in terms of the oxidative damage accruing to individual cells and organs. People who reach the age of 100 in good health often have a similar accumulation of damage to their DNA, lipids and proteins as people in poor health at the age of 50. To visualise the difference in simple terms, consider a population of cells exposed to radiation. Imagine that an average cell dies after it has taken 100 'hits'. If we now double the radiation intensity, the cells will accumulate 100 hits in half the time. They 'age' at twice the rate. Time is not an appropriate measurement of their age: the number of hits is far more relevant. In this instance, the number of hits reflects the biological age.

In this chapter, I will argue that biological age is central to our risk of disease. Our biological age equates to the number of 'hits' we have taken. This in turn depends on how we handle oxygen, or more particularly oxidative stress. In other words, old age is not a function of time, but a function of oxidative stress (which tends to rise over time). Thus, we ought to be able to prevent degenerative diseases if we can prevent oxidative stress. To find a cure for dementia, we should forget about the genes that increase our susceptibility to dementia, and look instead for genes – or other factors – that can protect us against oxidative stress. In so doing, we stand not only to prevent dementia,

but at the same time to ward off diseases like cancer and diabetes. In an age of health-care rationing, governments and pharmaceutical companies are spending billions of pounds a year on research and development, to create designer drugs tailored to individuals. There is a danger we are becoming obsessed with details and dismissive of important platitudes: we are all getting older in a rather similar way. The challenge of slowing ageing need be no more intractable than that of curing dementia, and there are some good reasons to think it may be more tractable.

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