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Growing old gracefully

Across the industrialized world, birth rates are falling and people are living longer. This will require a new focus on research to promote healthy ageing, rather than simply treating the diseases of old age. Alison Abbott reports.

Thomas More's *Utopia*, published in 1516, describes an egalitarian paradise free from the poverty and wanton greed of contemporary sixteenth-century European society. But its fictional citizens are still haunted by old age — "which as it carries many diseases along with it, so it is a disease of itself".

Given the gross inequalities of the day, More's idealized society required a formidable leap of the imagination. Now a small group of scientists from the unfashionable field of gerontology is urging us to consider a similarly radical leap. Today's utopian vision, they say, should be a society in which the elderly remain fit and healthy.

"People tend to associate old age with decrepitude and senility," says Rudi Westendorp, an expert on healthy ageing at Leiden University in the Netherlands. "But we have no reason to assume that weakness is inevitable in the old."

This message is a timely one, given the steadily ageing demographic in most industrialized nations. Advances in medicine have reduced the terrible toll of infant mortality caused by infectious disease, and more recently have started to overcome the killers of middle age, such as heart disease and cancer. Life expectancy is rising, and shows no sign of levelling off (see 'Three score years and ten … and more', opposite). At the same time, birth rates are falling, raising the spectre of societies that are unable to generate the cash to pay for the care of their elderly. There's an economic incentive, as well as a humanitarian one, for trying to break the link between old age and ill health.

Healthy outlook

At present, research into geriatric medicine is dominated by attempts to treat conditions, such as Alzheimer's disease, that mostly afflict the elderly. But with the demographic time bomb ticking loudly, politicians and research leaders are beginning to recognize the need to investigate the genetic and environmental factors that allow some people to remain healthy and active into their eighties, nineties and beyond.

The European Commission is now launching what will be the largest-ever study of the extremely old. The Genetics of Healthy Ageing (GEHA) project will gather genetic, health and lifestyle information on 2,800 pairs of siblings who are more than 90 years old, who will be compared with the same number of younger controls. The idea is to find out what genes the elderly brothers and sisters have in common, and which of these occur more frequently than in the general population.

And later this month, Germany's Max Planck Society is expected to approve the establishment of a new institute to study the factors that influence longevity in laboratory animals. Both approaches will be needed, experts say, if researchers are to devise drugs and other interventions that will promote healthy old age.

Research on model organisms such as the nematode worm *Caenorhabditis elegans* and the fruitfly *Drosophila melanogaster* has already shown that genes can influence lifespan. In one of the earliest, and most dramatic, demonstrations, researchers led by Cynthia Kenyon of the University of California, San Francisco, showed that mutations reducing the activity of a gene called *daf-2*, which among other effects seem to slow metabolism, could double the lifespan of

C. elegans[1]. Since then, studies in animal models have identified dozens of other genes that influence longevity[2].

But genes are only part of the story — as research on human populations has shown. Studies on twins indicate that only 25% of the variation in life span[3], and half of the variation in cognitive function late in life[4], can be attributed to genetic differences.

The rest is down to environmental and behavioural influences. So what can we do to increase our chance of living a long and healthy life? Not smoking is the most obvious piece of advice; moderating our consumption of saturated fats and alcohol is also likely to pay dividends. In rodents, diets that are extremely low in calories extend lifespan[5]. But it's not clear whether the same applies to people[6] — and who, in any case, wants to live on a near-starvation diet?

Indulgence in tobacco, drink and food can't fully explain the huge differences in length and quality of later life seen in most human populations. So if we are ever to devise individually tailored interventions to extend healthy lifespan, we need a more systematic view of the interactions between genetic and environmental factors that influence longevity. "There are lots of opinions and theories about how lifespan is determined at the molecular level, but few facts," says developmental biologist Peter Gruss, president of the Max Planck Society.

Systems failure

Most gerontologists believe that the deterioration associated with old age is caused by failures in multiple physiological systems, resulting from a variety of physical stresses. "We now think of ageing as strongly influenced by the way we lead our lives — an accumulation of different faults, unrepaired wear-and-tear, whose trajectory can perhaps be predicted from birth," says Tom Kirkwood, a gerontologist at the University of Newcastle upon Tyne, UK.

Ideally, human studies would follow the same design as those of model organisms, studying large numbers of individuals throughout their lives. But this is impractical, so researchers have typically either recruited cohorts of people who have lived to an unusually ripe age, or turned to historical data.

Archived information is often incomplete or unreliable, but Westendorp and Kirkwood have made use of the highly accurate and extensive records of births and deaths kept for the British aristocracy, showing that the longest-lived women tended to have fewer children[7].

This fits well with results from fruitflies, in which selective breeding for extended lifespan results in reduced fertility[8]— suggesting that there is a fundamental trade-off between reproduction and longevity. This is exactly what evolutionary biologists would predict: genes that promote youthful fertility should be favoured by natural selection, even if they cause problems in later life, after an animal's reproductive peak[9].

The trade-off is probably the result of a division of metabolic investment between reproduction and the repair mechanisms needed to fix general wear and tear. Genes in the *daf* family, for instance, help to regulate nematodes' cellular repair processes and signalling pathways that help to protect against stress-related damage[2].

A similar trade-off may operate in the immune system — with genes that promote our ability to ward off infections as youngsters being detrimental to health in old age. Claudio Franceschi of the University of Bologna in Italy has studied genes regulating the production of molecules called cytokines, biochemical messengers that help to regulate our immune responses. He has found that centenarians tend to have genes that favour the production of cytokines that damp down inflammation over those that promote it[10].

Inflammatory remarks

Franceschi has developed a theory that he calls 'inflamm-ageing', pointing out that many of the conditions that afflict the elderly are associated with inflammatory responses. "Low-level chronic inflammation is associated with all the classic diseases of old age, including Alzheimer's," he argues. High levels of inflammatory cytokines are also associated with the muscle weakness — known as sarcopenia — that often accompanies old age[11].

The inflammatory responses that in modern industrialized societies seem to restrict healthy longevity may have been selected for over most of our evolutionary history, when infections were rampant. To test this idea, Westendorp is now studying a population in northeast Ghana, where infectious diseases still cause appalling infant mortality. He is collecting mouth swab samples from newborn babies to determine whether the possession of genes for inflammatory cytokines correlates with survival. Westendorp is also studying cytokine genes in the oldest members of the same population, who should, if Franceschi's theory is correct, show less strongly inflammatory cytokine profiles.

Researchers are already planning clinical trials to see whether anti-inflammatory drugs can help to prevent diseases of old age. Some involve aspirin; others will test newer drugs that are more specifically targeted at the brain or other organs.

Franceschi's hunt for genes common to healthy Italian centenarians extends beyond the immune system. So far, he has looked at about 70 candidates, some of which are related to genes that have already been linked to longevity in model organisms; others were selected based on hypotheses about the likely causes of human ageing. Already, Franceschi has found several intriguing associations between extreme longevity and particular mutations, including some in genes that influence energy metabolism[12].

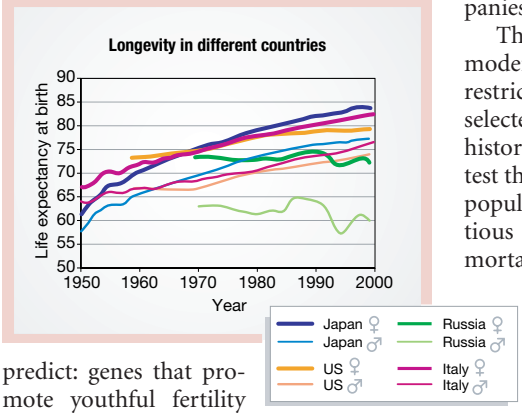
Other studies have looked at associations between longevity and genes involved in the metabolism of cholesterol, or its transport in

Three score years and ten ... and more

In the developed world, life span is continuing to rise (see Chart) — and given that the human record for longevity is 122 years, there's no suggestion that this trend should plateau any time soon.

Exceptional longevity tends to run in families, although whether this is primarily a result of shared genes or shared environment is unclear. And if you want to live a long life, it helps to be born female — or at least not to indulge in typically reckless male behaviour. "We reckon that one extra year is biologically inborn, and five or six years can be put down to differences in social behaviour between the sexes," says Rembrandt Scholz, a biomathematician at the Max Planck Institute for Demographic Research in Rostock, Germany. "Men take more risks — they drive cars faster, smoke more."

It also helps to be relatively wealthy. Trends in Russia, where male life expectancy tumbled during the hardships that followed the fall of communism, provide a stark reminder of the link between longevity and economic prosperity. **Alison Abbott and Anna Wellmann**



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S. STAMMERS/SPL

Mutations in the gene *daf-2* can double the lifespan of the nematode *Caenorhabditis elegans*.

the blood. The latter involves a series of lipid–protein complexes, or lipoproteins, of various sizes and densities. Blood cholesterol is typically measured in association with high-density lipoproteins (HDL) — 'good' cholesterol — and with low-density lipoproteins (LDL) — the 'bad' cholesterol that gets deposited in blood vessels, leading to cardiovascular disease.

Franceschi's team, for instance, has shown that certain variants of the gene for an enzyme that protects against the damaging effects of LDL cholesterol are more common in centenarians than in the general population[13].

One of the strongest associations is for variants of the gene for apolipoprotein E, a key component of the various cholesterol-carrying lipoprotein complexes. Those with at least one copy of the *ApoE4* form of the gene have a higher risk of cardiovascular disease and Alzheimer's disease in middle age. Centenarians are half as likely to carry this form as the general population, and are more likely to carry the *ApoE2* variant[14], which may protect against these diseases.

True or false?

One danger is that candidate gene studies may be throwing up false positive results, if the cohorts of long-lived people are not well matched genetically to control groups from the general population. To get round this problem, Nir Barzilai of the Albert Einstein College of Medicine in New York has studied Ashkenazi Jews, who are relatively genetically homogeneous. This makes it more likely that genetic differences between controls and the very old really are associated with longevity.

Barzilai measured the size of HDL and LDL complexes in the exceptionally old and their children, and compared them with control subjects who were the same age as the children. Larger lipoprotein complexes — which are believed to reduce the risk of cardiovascular disease — were more common in the exceptionally old and their offspring[15].

> "We'd like to understand how some people manage to avoid the diseases of ageing, so that we can help others who may not have a natural advantage to do the same."

Another approach to avoid false positives is to scan the entire genome for genes that promote healthy ageing without any prior hypothesis of what they might be. This can be done by analysing single-letter variations in the genetic code known as SNPs, or single nucleotide polymorphisms. If exceptionally old people share particular SNP variants, this suggests that a gene influencing longevity lies nearby.

Researchers led by Tom Perls, a specialist in geriatric medicine at Boston University School of Medicine, have used this approach to compare 137 sets of siblings, all more than 90 years old, with a control group from the general population. SNP analysis pinned down the location of one longevity gene to a small region of chromosome 4 (ref. 16). A subsequent detailed scan, led by researchers from Elixir Pharmaceuticals, a company in Cambridge, Massachusetts, that is especially interested in diseases of old age, implicated variants of a gene called *MTP*, thought to be involved in the production of lipoproteins[17].

The protein encoded by *MTP* has already been eyed up as a potential new target for cholesterol-lowering drugs[18]. Although the first generation of compounds was too toxic, gerontologists are excited about the possibility of extending healthy life by developing drugs to hit this target — or other parts of the pathways for metabolizing or transporting cholesterol.

The collaboration between Perls and Elixir will be dwarfed by the European GEHA study. In addition to their SNP analysis across 2,800 pairs of elderly siblings, GEHA researchers hope to collaborate with scientists at the Institute of Population Research at Peking University in Beijing. This would allow them to incorporate blood samples from about 3,000 ageing Chinese. "The more samples the better," says Bard Geesaman, Elixir's vice-president of medical development. "I'm not aware of any other study that is so ambitious."

The results won't be available for at least five years. But Westendorp predicts that GEHA will allow symptoms long regarded as an unavoidable consequence of ageing, such as sarcopenia, to be elevated to the status of treatable diseases, with known genetic and environmental causes. "We'd like to understand in detail how some people manage to avoid the diseases of ageing, so that we can help others who may not have a natural genetic advantage to do the same," agrees Geesaman.

It sounds like a utopian future, indeed. Let's hope that it proves to be more readily attainable than Thomas More's egalitarian social vision. ■

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Record holder: Jeanne Calment, who died in 1997, lived to be 122 years and 164 days old.

Alison Abbott is *Nature*'s senior European correspondent.

1. Kenyon, C., Chang, J., Gensch, E., Rudner, A. & Tabtiang, R. *Nature* **366,** 461–464 (1993).
2. Guarente, L. & Kenyon, C. *Nature* **408,** 255–262 (2000).
3. Skytthe, A. *et al. Twin Res.* **6,** 448–454 (2003).
4. McGue, M. & Christensen, K. *Exp. Aging Res.* **28,** 435–451 (2002).
5. Weindruch, R. & Walford, R. L. *The Retardation of Aging and Disease by Dietary Restriction* (Charles C. Thomas, Springfield, IL, 1988).
6. Heilbronn, L. K. & Ravussin, E. *Am. J. Clin. Nutr.* **78,** 361–369 (2003).
7. Westendorp, R. G. J. & Kirkwood, T. B. L. *Nature* **396,** 743–746 (1998).
8. Zwaan, B. J., Bijlsma, R. & Hoekstra, R. F. *Evolution* **49,** 649–659 (1995).
9. Kirkwood, T. B. L. & Austad, S. N. *Nature* **408,** 233–238 (2000).
10. Franceschi, C. & Bonafè, M. *Biochem. Soc. Trans.* **31,** 457–461 (2003).
11. Visser, M. *et al. J. Gerontol.* **57,** M326–M332 (2002).
12. Rose, G. *et al. Exp. Gerontol.* **38,** 1065–1070 (2003).
13. Bonafè, M. *et al. Eur. J. Hum. Genet.* **10,** 292–296 (2002).
14. Schachter, F. *et al. Nature Genet.* **6,** 29–32 (1994).
15. Barzilai, N. *et al. J. Am. Med. Assoc.* **290,** 2030–2040 (2003).
16. Puca, A. A. *et al. Proc. Natl Acad. Sci. USA* **98,** 10505–10508 (2001).
17. Geesaman, B. J. *et al. Proc. Natl Acad. Sci. USA* **100,** 14115–14120 (2003).
18. Jamil, H. *et al. J. Lipid Res.* **39,** 1448–1454 (1998).