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Faculty of Public Health Medicine Queen Elizabeth The Queen Mother Lecture

Germs, Genes and Greenhouse Gases: The Changing Landscape of Population Health

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Foreword by James McEwen and John Wyn Owen

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Foreword

Public health has rightly always had a commitment to learn from the past and to use this knowledge to look to the future. This lecture not only does this but reminds us that some of the problems of the past are just as relevant today. It also reviews some of the new issues in health. Even more critically, it seeks to move forward our way of thinking and understanding the developments in science, since some of our present ways of understanding and interpreting scientific evidence, with respect to population health are limiting.

It is often said that a lecture is challenging, and indeed this one is, covering aspects of infection, environmental hazards, genetic advances and pollution. But it is more than challenging, in many ways it is disturbing and is designed to ensure that we do not remain complacent. Epidemiologists and all who work in any aspect of public health must face up to the challenges with respect to broadening their understanding of issues, and give active consideration of what should be done with respect to the solutions that are put forward in this lecture.

This is an exciting lecture, covering many aspects of particular relevance today. For all who are committed to improving population health, this should be required reading.

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Tony McMichael is a medical graduate from Adelaide. He is currently Professor of Epidemiology at the London School of Hygiene and Tropical Medicine, United Kingdom, with previous appointments at the University of North Carolina, CSIRO Division of Human Nutrition, and the University of Adelaide. His research interests have encompassed occupational diseases, diet and cancer, and environmental epidemiology (effects of environmental lead exposure on child cognitive development, aetiology of cataracts and quantitative environmental health-risk assessment). He has been an adviser to WHO, the UN Environment Programme and the World Bank. During 1990–1992 he chaired the Scientific Council of the International Agency for Research on Cancer (WHO).

During the 1990s he focussed on assessing the population health risks from global environmental change. Current research activities include studies of dietary factors in breast cancer, heat-wave impacts on urban mortality patterns, and modelling climate change impacts on population health. Since 1994 he has chaired the international scientific assessment of potential health impacts by the UN's Intergovernmental Panel on Climate Change. He is a member of WHO's Advisory Committee on Globalisation and Health, a Council member of the newly formed World Health Policy Forum (focussing on food and health policy) and co-editor of the journal *Global Change and Human Health.* In 1993 he published *Planetary Overload: Global Environmental Change and the Health of the Human Species* (Cambridge University Press). In 2001 Cambridge will publish his book *Environments, Societies and Patterns of Disease: Footprints to Uncertain Futures.*

It is a special, and double, honour to be asked to give this Queen Elizabeth The Queen Mother Lecture in this year 2000. First, the Queen Mother is about to turn 100 – entering her second century. Second, we are all entering a new century on the calendar, indeed a new millennium. It is therefore an opportune moment to look backwards over a century or so of public health, and to look ahead to the coming century.

Engaging with a complex set of issues and choices

The reason for taking stock is not just to do with these pleasingly rounded centenarial numbers. It is because we stand at an unusually complex crossroads in our pursuit of better ways of studying, improving and maintaining the health of populations. We face three contrasting facets of the future.

1. *The rise of "post-genome" science, which will reinforce notions of specificity of "cause" and of preventive and therapeutic response.* We can anticipate a rapid proliferation of "post-genome" science. This has the potential to transform medical and public health practice.
2. *The renewed interest in the social causation of disease, seeking to elucidate the broader contextual influences on disease patterns and health inequalities.* There is a renewed interest in studying and ameliorating the persistence of social-economic disadvantage as a fundamental cause of health inequalities – within and between countries.
3. *The advent of global environmental change as a health hazard, engendered by humankind's exceeding of the biosphere's limits.* There is a rising awareness of the environmental limits to the expansion of human economic activity, and of the adverse health consequences of disrupting the biosphere's ecological systems and other great biogeochemical systems (such as world climate).

I will argue that there is a need for us in public health science to embrace a more integrated and interdisciplinary approach; to think in "ecological" terms about the social and environmental systems which bear upon patterns of human health and disease (McMichael, in press). Most of the big problems that we face today are not amenable to single-discipline reductionism. Indeed, various commentators have

recognised a more general need for the reintegration of the biological sciences. In an interesting paper entitled "Journey to the Center of Biology", published recently in *Science*, Lander and Weinberg (2000) argue that there is now a great need to seek an integrating, reconstructive type of biological science to replace the reductionist and mono-disciplinary paradigm that has long predominated.

There is, I suggest, a need for an ecologically-based understanding of how the natural environment and the social environment affect patterns of health and disease. Public health, as all here appreciate, is about the health of populations – populations not as aggregates of free-range individuals, but as organic collective entities with complex, structured histories, cultures and internal social and economic relations. Populations, properly, are our main focus of analysis, of concern. An ecological perspective allows recognition of influences and processes at different levels of organisation; it recognises the interdependencies between humans, other species and the physico-chemical environment; and it acknowledges that complex systems are dynamic, feedback-rich and beset by non-linearities.

Yet that population perspective is coming under challenge from the virtuosity of molecular biology, genetic typing, and the new possibilities for individual genotype-based management of risks to health. We can understand these challenges better by looking at two nineteenth-century analogues for emerging contemporary trends. However, to remind ourselves of the constraining effects of prevailing theory, prevailing paradigm, first let us look back much further in time – to a man who *was* much impressed by pleasingly rounded numbers.

Pythagoras

Around two and a half thousand years ago Pythagoras was born on the Greek island of Samos. This island was on the fringe of the Ionian civilisation, the cradle of Greek philosophy and science. Pythagoras had unorthodox social ideas that brought him into conflict with the autocratic ruler of Samos, Polycrates. So he and his followers fled to Croton in southern Italy.

Numbers, said the Pythagoreans, were the natural manifestation of order in the universe. With one dot you get a no-dimensional point; with two dots a one-dimensional line; with three dots a two-dimensional triangle; and with four dots a three-dimensional pyramid. Add the

1, 2, 3 and 4 together and you got the special number 10. Take the ratios of 2:1, 3:2 and 4:3 and you get, from a taut string, the three most important musical intervals – an octave, a fifth and a fourth. A right-angled triangle with short sides of 3 and 4 units length had a long-side (hypotenuse) of 5 units. Square the 3 and the 4, add them (i.e., 9 plus 16), and you would get the square of the hypotenuse (25). Here was a way to construct a cosmology into which all observations, ideas and theories would fit, a unifying Theory of Everything.

The Pythagoreans also had rules of correct daily living. One rule was to avoid eating fava beans (the type of beans that are routinely served with cold salads on Greek islands today). Indeed, they even avoided inhaling the pollen from a flowering bean field.

This stricture against eating beans may have had several origins. Diogenes, who wrote rather colourful histories of predecessors, ascribed the stricture to the Pythagoreans' belief that beans, as part of the cosmos, were likely to be the vehicle of transmigrating souls. Since the eating of beans induced flatulence, the diner might well be inadvertently deflating the spirit of the transmigrating soul – perhaps of a close, recently deceased relative.

The alternative explanation is that the Pythagoreans understood that some individuals were adversely, sometimes fatally, affected by eating beans. Presumably they attributed this to some bean-induced imbalance of bodily humours. We now know that this disorder, entailing haemolytic crisis, was due to a genetic adaptation to malaria, then prevalent around the Mediterranean coast. The enzyme deficiency that rendered the red blood cells non-nutritious for the malaria parasite also prediposed the cells to damage by metabolites from digested beans.

Pythagoras himself apparently suffered – indeed perished – from this particular enzyme (glucose-6-phosphate dehydrogenase) deficiency. Having enraged the local Croton populace with his outspoken political views, he was obliged to flee for his life. Unfortunately his escape route entailed negotiating a bean field. As he ran around the right-angled boundary of the field, his irate pursuers sped across the hypotenuse, caught him and fatally assaulted him.

Now, the point of this diversionary story is that, in all cultures, humans find ways of explaining their experiences of illness and disease. We frame such explanations in relation to our

culture and our stock of "knowledge". Our accounts of illness and disease thus have coherence within our own immediate cultural frame. The miasma theory, the germ theory and the theory of chemical carcinogenesis have all constrained scientific imagination; they have, during their ascendancy, limited the range of alternative explanations.

Today, we are constrained by the legacy of classical Newtonian science, reflected in the linear and mechanistic thinking of the biomedical model, and by the reductionism that is intrinsic to RCTs. We have little appreciation that the population's profile of health and disease is, in the long run, a reflection of ecological circumstances. Yet, as global environmental changes begin to press upon us, we need to think in larger-scale population-level terms about patterns of health and disease. The idea that, at a global level, we might be overstepping the limits of the natural world is, historically, a novel one. Just as, for Pythagoras, the idea that favism was due to a genetic adaptation was outside his frame of reference.

So, let us return to the two more recent historical analogues of present ideas, or values, in public health and biomedical research.

Two historical analogues of present trends

1880s–1920s: Germ Theory – The ascendance of specific, reductionist, causal explanation

Public health entered the twentieth century straddling two different views of epidemic disease. The older view had its origins in the Hippocratic idea of "miasmas" in which disease was intimately linked with the quality of the natural environment. The newer view grew out of the Pasteurian revolution and Robert Koch's postulates: henceforth all epidemic diseases were to be understood as having a specific microbial origin.

A focal time in the evolution of this dialectical struggle, in Europe, had been the late 1840s. Ignaz Semmelweiss, in Vienna, had shown that there was a transmissible agent that caused puerperal fever. John Snow, in London, was marshalling evidence that cholera was caused by a water-borne transmissible agent. The devastating Irish Potato Famine of 1845–46 had led plant scientists towards the view that there was a transmissible agent that caused the fungal disease; the blight was not a mere consequence of withered plants. Meanwhile, however, the miasmatists held sway. Edwin Chadwick, in England, proposed

far-reaching sanitary reforms in the general belief that diseases were caused by non-specific environmental filth and its pervasive emanations.

With the rise of the Germ Theory in the 1880s, the several following decades initiated an era that brought greater changes in the practice of medicine and public health than had occurred at any other time in history (Duffy 1990). Developments in bacteriology, pathology and physiology were combined with rapid advances in other related scientific fields.

The initial impact of the germ theory was, inevitably, reductionist. It enabled the overthrow of non-specific miasmatic environmental explanations of disease by a theory of specific causation of disease. Here was the wellspring of the hugely influential biomedical model. Arising from the germ theory, the elucidation of vitamin deficiency disorders and the identification of several specific cancer-causing occupational exposures, physicians now had a view of disease and its treatment that seemed to render public health's broad social and environmental agenda unnecessary. Disease was at last uncoupled from its social roots. The focus was now on individual diseases and individual patients.

In a recent paper in the American Journal of Public Health, Brandt and Gardner (2000) write: "The reductionism of the medical model, its insistence on mechanism and universal pathophysiology, directly contradicted long-standing assumptions in public health about the significance of the social environment and behavior in the production of disease." This shift in focus was reflected by Dwight Chapin, a leading US advocate for "The New Public Health", who in 1911 argued for the primacy of specific preventive measures against infectious diseases. Health departments, he said, should desist from their assorted generic social and environmental interventions, since it was more important to elucidate the specific mode of transmission of each infection and to identify the vulnerable aspect of the process.

We see in this a clear analogue to the specific and deterministic views of today's proponents of post-genome science. They see in the new molecular genetics the opportunity to prevent disease at its molecular source by germ-line therapy, or to modify risks to health either by somatic gene therapy or by the detection and counselling of high-risk individuals.

Mid-nineteenth century: Market forces, environmental decline, health hazards, and policy imperviousness

The mid-nineteenth century in Britain and elsewhere in Europe was an era of laisser-faire economics and widespread environmental blight. Indeed, the modern public health revolution began in European cities in the nineteenth century where, under the pressures of industrialisation, poverty, crowding and the breakdown of traditional ways of living, the conditions of daily life had deteriorated for the mass of people – while the better-off fled to the suburban periphery (Szreter, 1997). This process characterised the middle decades of nineteenth-century England, during which the suburban well-off largely ignored the plight of the urban poor. The resultant policy stasis and the growing crisis of urban poverty, disease and overflowing work-houses precipitated Edwin Chadwick's famous *Report on the Sanitary Condition of the Labouring Population of Great Britain* (Flinn, 1965).

Chadwick argued for engineering interventions to arrest environmental degradation. Even so, within the prevailing *laisser-faire* ethos, the oft-struggling middle-class representatives of inner urban electorates were too preoccupied with the immediacies of commercial survival to embrace ambitious urban improvement schemes. Hence Chadwick's centrally-controlled programme met widespread resistance from unsympathetic local political interests. The impasse was eventually remedied by the decentralisation of sanitary powers to local municipalities via the Sanitation Act of 1866 (Szreter, 1997; Chaplin, 1999). In the ensuing three decades urban authorities in England transformed the provision of sewage and water services from private enterprises into public services.

This energetic municipal-level action was reinforced by the recognition by the better-off that diseases, such as cholera, were no respecters of persons. In earlier decades, when diseases such as typhoid, typhus and the routine diarrhoeal diseases were largely confined to the urban poor, the comfortable middle class could afford to ignore them. However, the succession of four cholera epidemics in England from the 1830s to the 1850s made clear that the decline in urban environmental conditions was posing new and unpredictable threats to all and sundry, rich and poor. Further, there were fears of economic downturn if disease and disorder spread, and, in turn, fears of political unrest (especially in the

wake of the 1848 turmoil in continental Europe). Accordingly, the need for urban sanitary and administrative reform was widely accepted (de Swaan, 1988).

We can see in this an analogue to global climate change and the attendant risks to society and public health. The cause of global climate change lies in the accelerating increase in the emission of greenhouse gases as a result of expanded human economic activity in recent times (IPCC, 1996; UNEP, 1999) – the expansion of the global human footprint. Further, in recent decades, as the process has escalated, we have had an increasingly deregulated globalised economy in which the free-market ethos has been ascendant.

The current situation is as follows:

- Continuation of greenhouse gases build-up, despite general recognition of the cause of the problem – and despite a growing understanding of the range of likely consequences, including adverse population health impacts (McMichael and Haines, 1997). This includes the recognition that adverse impacts will tend to be concentrated in poor and vulnerable populations, and particularly in tropical/subtropical regions.
- There is an incipient readiness by western European countries to take pre-emptive action – albeit at the level agreed at the 1997 Kyoto Conference, a level that is far below the emissions reduction necessary to arrest the problem. However, there is still strong resistance by the US (the major national source of GHG) to taking any action that might entail economic loss – or that might cede advantage to less developed countries (e.g. China).
- Meanwhile, there are some signs of international bottom-up restiveness regarding the processes and consequences of economic globalisation and the concentration of wealth and power – e.g. the WTO Battle in Seattle (1999); the coordinated resistance to the socially menacing Multilateral Agreement on Investment; and continuing debates over the potential hazards of GM foods.

Thus we see a clear parallel. In each of these two situations:

1. The environmental problem was amplified by the values and practices associated with *laisser-faire* economics.
2. The privileged segment of society was initially indifferent to the

threat and to the adverse impacts on the under-privileged.

3. Subsequently, as insight grows, as democratic processes strengthen and as unadorned economic fundamentalism is supplemented by a mix of enlightened self-interest and acceptance of moral responsibility, collective action is taken to remedy the environmental problem.

So, we have identified historical analogues for two of today's main trends – the rise of a specific, reductionist theory of causation (germs in the late nineteenth century; genes now), and the eventual social response to a generic deterioration in environmental conditions understood, in broad ecological terms, to pose widespread risks to population health (miasmatic influences in mid-nineteenth century; global environmental changes now).

Now, let us look a little more closely at the three main topics: Germs, Genes and Greenhouse Gases.

Germs

I have already described the advent and influence of the Germ Theory. This theory nurtured the classical "magic bullet" approach that characterised the biomedical model. The further development of the rudimentary ideas of ecological relationships, of systems-based phenomena, was thereby eclipsed.

It is not surprising, then, that we have encountered unforeseen problems of genetic resistance with our reliance on antibiotics and pesticides. Our often profligate use of these agents displayed considerable ecological naiveté. This naiveté was also evident in the unseeing remarks of various senior authoritative scientists around 1970 to the effect that the era of infectious disease in developed societies was now over. Those remarks were uninformed by an awareness of the inherent lability and opportunism of infectious disease agents, by their irrepressible ecological opportunism.

We have come to understand much better in recent decades that all changes in human ecology – be they urbanisation, migration, contraceptive practices, sexuality, food production, land clearance, water management, evaporative air conditioning, or the spread of poverty – alter the ecological opportunities for microbes. HIV/AIDS has been a tragic reminder of the centrality of social determinants, especially of poverty and ignorance, in the causation of infectious disease.

We have seen plenty of other recent examples of infectious diseases either emerging or resurging in response to changes in human ecology. The list includes:

- Human infections due to intensive food production:
  The BSE and nvCJD episode in the UK.
  The Nipah virus in Southeast Asian pig-farming.
  The mobilisation of forest-based haemorrhagic fever viruses in Latin America.
- The rising incidence of various sexually transmitted infections – including herpes virus infections and chlamydial infection.
- The spread of several major vector-borne infectious diseases, including malaria and dengue fever.
- The resurgence of infectious diseases of poverty, especially tuberculosis.

To think about infectious diseases in short-term and piecemeal fashion, neglecting both the wider social context and the system interactions likely to flow from our actions, is to risk adverse public health outcomes. The values of the private sector, necessarily focused on profitability, do not encompass these wider considerations. That is the task of clear-visioned public health professionals working in conjunction with enlightened government.

Genes

We come next to genes: the topic of the moment; the subject of a thousand newspaper headlines over the past month; indeed the icon of modern biological science. As I argued earlier, and by analogy to the Germ Theory, the advent of post-genome science will reorient our thinking to the specific, the reductionist, and the individual.

There is no doubt that molecular genetics can further empower epidemiological research. Consider the tantalising question of neural tube defects. We know from earlier British trials that folate administration can prevent around three-quarters of neural tube defects. But we also know that there are various other teratogenic exposures – alcohol, dextromorphan, anticonvulsant drugs and others. The recent identification of the NMDA receptor in cells as a "candidate gene" involved in neural tube defect aetiology has depended on recognition of the fact that many known teratogens impede NMDA receptor function. The gene product, the NMDA receptor, provides a final

common pathway for a set of otherwise disparate putative teratogens. It thus heightens our confidence in the identity of those various teratogens.

However, the scope of post-genome research and social application is vast. There are many issues for public health. Before considering just a few of them, let us look at the brief history of this topic.

Preparing for a post-genome world

Gregor Mendel deduced the essence of genetic inheritance over a century ago. The basic molecular structure of the double helix of complementary nucleotides was cracked a half-century ago. Today we are entering a "post-genome" age in which we are learning the molecular geography of the genes and have the techniques to induce specific mutations in those genes. We, the product of natural selection, are about to become the comptrollers of artificial selection.

We can modify the molecular structure of genes, insert genes from one species into another thereby producing transgenic organisms, and clone whole animals. By combining those last two techniques, we anticipate mass-producing transgenic organisms such as cows that make vaccine proteins in their milk to immunise young milk-consuming humans. We look forward to successful gene therapy for diseases with simple genetic causation. We recognise, nervously, the possibilities of genetically-modified designer babies.

Biology has thus been transformed. Today the gene is the centrepiece of biotechnology and has become a cultural icon. Molecular genetics, say its proponents, will transform the preventive and curative dimensions of medicine, will provide an alternative view of the nature and causation of disease. The Human Genome Project has been hailed as a directory of disease determinism – a manual for the personalised management of genetically-based risks of disease.

This idea of biological determinism remains very contentious. Its critics argue that we cannot understand the behaviour, the dynamics, of complex wholes from the analysis of disaggregated parts (Lewontin, 2000). The champions of molecular genetics disagree, arguing that if we can "reduce" finely enough then we can achieve causal exactitude. Among the more enlightened molecular biologists one can hear increasing attention being paid to the idea of collective gene action, to the notion of interactive clusters of genes that are themselves

a "package" product of evolution. We are thus moving beyond the genetic fundamentalism of the *Selfish Gene*.

Epidemiologists cannot ignore this debate. There is a need to keep genes in perspective relative to the many non-genetic determinants of human disease. There is a particular need to explore the interaction between genetic susceptibility and environmental triggers. In the absence of obesity, for example, any population differences in inherited patterns of insulin sensitivity have little impact on the occurrence of clinical Type II diabetes.

Gene-environment interactions

For the great majority of genes, gene-environment interactions are very often the critical determinant of disease risk. We identified such an interaction several years ago in a case-control study of dietary factors in colon cancer, conducted in Adelaide, South Australia (Roberts-Thomson *et al.*, 1996). There is a gene, the *NAT2* gene, that determines whether each of us is either a fast or a slow acetylator. If you are "fast", then you can drink coffee at midnight and be asleep soon after. If you are "slow", the unmetabolised caffeine will keep you awake. The same enzyme pathway also activates certain arylamines that occur in food, especially in cooked meat – and especially at an Australian barbecue. In our study we found that not only was there a modest increase in risk of colon cancer associated with frequent meat consumption, but that the risk was clearly greatest in those meat-eaters who were also fast acetylators. Among the slow acetylators, frequency of meat consumption showed little relationship to risk of cancer.

There are many other such examples, including the interaction of the Apolipoprotein E e4 allele and alcohol in the causation of cognitive impairment (Dufouil *et al.*, 2000) and mutations of the vitamin D receptor (VDR) gene and calcium intake in the causation of osteoporosis (Kral *et al.*, 1995).

Screening – Number Needed to Screen (to prevent one case)

Another major public health issue is that of genetic screening. Many disorders, most of which occur infrequently, are entirely or largely caused by strong single-gene effects. However, the most common diseases, and those that show strong trends over time and migration, entail complex traits with polygenic determination. This includes hypertension, insulin resistance, dyslipidaemia, mental depression, and so on. There may be around 400 genes that affect carcinogenesis.

Clearly, when there is a multiplicity of weakly-acting genes, each dependent on a complementary exogenous exposure for their expression, then the configuration of environmental exposures is the dominant determinant of disease occurrence.

An example is that of hereditary haemochromatosis (Motulsky and Beutler, 2000). This iron-storage disorder affects about 1 in 3,000 Caucasians. Homozygosity for the C282Y allele carries a relative risk of 4,400, and accounts for three quarters of cases. But this particular genotype occurs in only about 1 in 5,000 persons. Therefore screening would only be justified in high-risk families.

A better-known example of the controversy over genetic screening is in relation to breast cancer – the BRCA1 and BRCA2 genes. These two genes, when normal, must play an important biological role since they have been conserved essentially unchanged for 50 million years across diverse mammalian genera. The two mutant genes occur relatively rarely – in about one in every 800 women – but they each increase the risk of breast cancer more than ten-fold (Burke *et al.*, 1997). Nevertheless, being rare, they account for only around 4 per cent of breast cancers in western populations. In contrast, within high-risk families these genes account for around 80 per cent of all breast cancers.

Now, it is in the nature of biological evolution that single and strongly deleterious genes will be selected against. Therefore, all such "BRCA" type genes (e.g. Huntington's Chorea, cystic fibrosis) are rather rare. This inflates the Number Needed to Screen (NNS) in order to prevent one case of disease. To prevent one case of breast cancer by screening for the BRCA1 mutant, it is necessary to screen 2,500 women from the general population. (Note, however, that this number contracts sharply to 5 women if screening is confined to very high-risk families.)

On the other hand, conditions which are polygenic – e.g. diabetes and hypertension – are influenced by many weak genes. By early 2000, about 15 genes for obesity had been identified and around ten for osteoporosis. Such genes evoke much less selection pressure from natural selection, and therefore tend to be more prevalent within the population. However, the number needed to be screened is still relatively high because of the small increment in risk associated with each such variant gene. For example, the risk of lung cancer in smokers increases by a modest 30 per cent if they have the

defective allele for the metabolising enzyme, glutathione-s-transferase. Therefore, in order to detect one pre-clinical case of lung cancer it would be necessary to screen around 35 smokers for this allele – a number that is not much less than the number of general population (smokers and non-smokers) that would need to be screened to detect one such case (Vineis *et al.*, in press).

Clearly, at least for logistic and cost reasons, we should not rush into genetic screening. Finally, a brief comment about the other major ethical concern – the prospect of genetically modified humans.

Genetically modified humans

The quest for somatic gene therapy has begun, with immune deficiency disorders and cystic fibrosis. The prospect of germ-line gene therapy is becoming more feasible. Where somatic gene therapy does running repairs on selected body cells of an extant individual, germline gene therapy changes the heritability of genes between generations. The fertilised egg is the likely target of germline therapy.

Earlier this year, the well-known American scientist, Freeman Dyson, wrote: "If we allow a free market in human genes, wealthy parents will be able to buy what they consider superior genes for their babies. This could cause a splitting of humanity into hereditary castes. Within a few generations, the children of rich and poor could become separate species. Humanity would then have regressed all the way back to a society of masters and slaves. No matter how strongly we believe in the virtues of a free market economy, the free market must not extend to human genes ... The two great evils to be avoided are the use of biological weapons and the corruption of human nature by buying and selling genes." (Dyson, 2000.)

Now, before we reject this scenario as science fiction, recall that the gap between rich and poor has widened from a 20-fold gap in 1960 to an 80-fold gap now. Wicked people did not set out to widen that gap; it simply happened because of the way our market-based, growth-oriented economy works. Great social changes can occur insidiously and unintentionally.

We must be quite clear about the implications of germline therapy. It is a way of altering, permanently, the human genetic code. Humans, thus, would become genetically modified organisms. For the moment, our society rejects the idea of "designer babies". But it is only a quarter-century since we rejected the unsettling, even abhorrent, idea of

in vitro fertilisation – and that procedure is now common.
I anticipate that we will readily agree to use gene therapy to eliminate genetically-based disease. However, we may well prefer not to programme body height and shape, not to modulate personality and intelligence, and not to converge upon an idealised set of "perfect" genes. It is likely, I think – and hope – that we will opt for continued human genetic and phenotypic diversity, and thus retain the essence of being a species.

Greenhouse Gases

The aggregate impact of greatly increased human numbers and escalating intensity of economic activity has begun to exceed the limits of the ecosphere. The ecosphere comprises the biosphere, wherein life exists, plus its supportive systems – such as the climate system, the stratospheric ozone layer, and the deep oceans that distribute equatorial heat around the globe. This unprecedented occurrence has arisen essentially during our lifetimes, as various thresholds have been exceeded.

The large-scale and unfamiliar, human-induced, environmental changes to Earth's biogeochemical systems include:

1. Global climate change.
2. Stratospheric ozone depletion.
3. Amplified elemental cycles: excessive bioactive nitrogen and sulphur.
4. Biodiversity loss.
5. Spread of invasive species.
6. Degradation of food-producing resources (terrestrial and marine).
7. Depletion of freshwater sources.
8. Dissemination of persistent organic pollutants (POPs).

These changes reflect a first-ever capacity of humankind to overload Earth's "sinks" and to over-exploit Earth's "sources", thereby causing non-compensable changes in planetary processes. The first three of these are unprecedented in the sense that they entail integrated disruption of global environmental systems. The latter five have now also become "global" in scale, although they arise via multiple local impacts that cumulate to global changes.

Intriguingly, Goethe foresaw the present crisis in his greatest play, Faust, published in 1832 (Binswanger and Smith, 2000). He assessed that the industrial revolution and the economic growth that it generated would lead to increasing exploitation

and subjugation of the natural world. Faust, whom Goethe presents as the representative modern man, embarks on an ambitious project of economic progress, symbolised by the building of a great dyke to reclaim land. The play warns that this human intervention, embarked on by Faust, may have unforeseen and tragic consequences. Nature, Goethe tells us, reacts according to its own laws – laws which humans can never fully predict. With a blindness born of hubris, Faust wagers with the Devil that he can succeed, that he can push back Nature for the good of humanity. The Devil, Mephistopheles, knows better.

Since many of today's global environmental changes are disrupting ecological and biogeochemical systems that underpin or otherwise influence human health, changes in the pattern of human disease are likely to result.

Potential health impacts of climate change and ozone depletion

Global climate change will occur – and most probably is already occurring – because of the human augmentation of greenhouse gases in the lower atmosphere. Average world temperatures have increased over the past quarter-century by around 0.4°C. Other changes in physical and biological systems – glaciers, plant migration, animal behaviours, disease outbreaks in nature – corroborate this change in world climate. The UN's Intergovernmental Panel on Climate Change forecasts an increase of 2–3°C over this coming century. This would represent a rate of increase about 20 times faster than occurred during the environmentally hectic period after the last ice age between 15,000 and 10,000 years ago (McMichael, 1993).

Questions about the future health consequences of climate change are therefore now firmly on our environmental health agenda.

Global climate change would affect human health via paths of varying complexity, scale and directness. The timing of the various impacts would also differ. There would be both positive and negative effects, although expert scientific reviews assess that the latter would substantially predominate (McMichael *et al.*, 1996; Haines *et al.*, 2000). The more direct health impacts of climate change include those due to changes in exposure to weather extremes (heatwaves, winter cold), those due to increased production of certain air pollutants and aeroallergens (spores and moulds), and those due to increases in other extreme weather events (floods, cyclones, storm-surges,

droughts). Via more complex and essentially indirect mechanisms, climate change would affect infectious disease transmission and regional food productivity (especially cereal grains – likely to be adversely affected in several already food-insecure low-latitude regions). In the longer term, it is probable that these indirect impacts on human health would be of greater magnitude than the more direct impacts.

Epidemiologists face a major challenge in estimating these potential health impacts. This requires working from modelled scenarios of future environmental conditions – e.g. world climatic conditions for the decades of the 2020s and 2050s – to which we apply our existing knowledge of how climatic variation affects some particular health outcome. For example, if we know how death rates in British cities are affected by heatwaves in today's world, we can estimate how they would respond to a summer season in a future warmer world in which the frequency of heatwaves is, say, tripled.

A more complicated task is to estimate how climatic changes would affect the potential geographic range of transmission of mosquito-borne infectious diseases such as malaria and dengue fever. Considerable developmental effort has recently gone into building and testing mathematical models for making such projections. The models in current use have well-recognised limitations – but they have provided an important start. For example, from multiple modelling runs by computer it seems likely that malaria will significantly extend its geographic range of *potential* transmission during the twenty-first century, as average temperatures rise by several degrees centigrade and as regional rainfall patterns change.

Meanwhile, higher in the atmosphere, depletion of stratospheric ozone by human-made gases such as chlorofluorocarbons (CFCs) is certainly already occurring. As a result, ambient ground-level levels of ultraviolet irradiation are estimated to have increased by up to 10 per cent at mid-to-high latitudes over the past two decades. Scenario-based modelling, similar to that described above (albeit for a simpler system that is not based on changes in responses of living organisms), indicates that European and US populations will experience a 5–10 per cent excess in skin cancer incidence during the middle decades of the coming century (Slaper *et al.*, 1998).

Solutions

Finally, a brief word about approaches to solving these challenges.

Most fundamentally, we need to think more in systems terms. Reductionist models in experimental science and the general prominence of the biomedical model have carried us a great distance already; and they will continue to advance our understanding. However, the world is much more complex than such reductionism allows. Hence, there is a need to widen our scientific repertoire of concepts and methods. Indeed, there are signposts evident already. The recent renaissance of integrative thinking, and the advent of systems-based modelling, holds promise of developing a more "ecological" approach to many important and diverse topic areas in public health.

The following are examples of this type of systems-based thinking:

- Assessment of the foetal/infant origins of adult disease, and the extension of this concept into a life-course model of disease risk evolution.
- Recognition of the pervasive environmental spread of persistent pollutants, and of their impacts on human and non-human organ systems: reproductive, immune and central nervous systems.
- Wilkinson's ideas about "Unhealthy Societies", in which the afflictions of income inequality operate, at least in part, via impacts on social cohesion and mood that affect health outomes (Wilkinson, 1996).
- Recognition of the importance of social infrastructure (literacy, democracy, equity, civil institutions) as prerequisite to achieving effective public health interventions.

We need to achieve integration of the mechanistic insights of molecular biomedicine with an ecological understanding of the human/society/ecosystems/biosphere interface. Consider these two examples.

Example I: How best to deal with obesity?
The recent rapid rise in obesity (WHO, 1999) cannot, of course, have been due to population genetic change. It is the result of radical changes in the way we live: the transformation of the diet in industrialised, wealth-accruing populations, and the spectacular reduction in levels of physical activity that characterised the

twentieth century in those populations. The main remedial options therefore include: increases in physical activity levels; better food and nutrition policy; personalised lifestyle management; and genetic/phenotypic modulation.

Obesity-prone individuals could be identified, genotypically, and given personalised counselling. However, reliance on individual interventions within an otherwise obesity-inducing social environment would commit us to the indefinite continuation of individual interventions across successive generations. This would be very costly to society. How much better to achieve enduring solutions through the one-off arighting of human ecology. Hence, we must take the bigger view which seeks to combine improvement of population diet and the environmental attributes that determine patterns of physical activity, as population-level strategies, with personalised counselling.

Example II: Feeding an expanding human population: enlightened use of genetic biotechnology

Genetic engineering can be used for making food production and sales more profitable for suppliers and large commercial farmers – or it can be used to achieve nutritional gains in food-insecure and malnourished populations. Via genetic engineering, pre- and post-harvest losses could be reduced; nutritional quality could be improved (e.g. micronutrient enrichment of rice); and vaccination proteins could be incorporated in certain foods.

This raises the prospect of genetic biotechnology being used for social benefit, as the centrepiece of a new "Green Technology". Historically, new "green technology", in the form of agrarianism and animal breeding from ten thousand years ago, allowed human populations to greatly increase their size, although not their life-spans. In recent centuries "grey technology" has supervened, as industrialisation has transformed human ways of living. This industrialisation has accelerated material wealth creation, increased life expectancy, allowed further population expansion, stimulated the proliferation of cities, factories, motorised transport systems and supermarkets, and caused widespread environmental damage. That damage is increasing, and much of it is becoming irreversible – or only very slowly reversible. Today, however, we have the opportunity to apply new genetic biotechnologies in ways that will benefit human health, improve human nutrition, increase the

capture of solar energy in renewable energy technologies, and amplify the sustainable production of various useful non-food proteins and other natural products.

The great political and ethical challenge will be to find ways of applying our new and ingenious biotechnologies to solving the world's great social, environmental and public health problems. We in the public health profession must be alert to the potential inequities, resource diversions, and non-sustainable practices that might all too readily flow from commercialised applications of new genetic knowledge. We must be alert to new inequalities in the provision of health care, to the tensions between individualised preventive strategies and the reduction of health hazards in the wider social and natural environments, and to cooption of the new genetic technologies into further aggressive economic expansion that weakens the world's life-support systems.

Conclusion

Human biology has been shaped by long slow evolutionary pressures, stretching back through millions of years of hominid adaptation in a changing environment. Human society, especially over the past 10,000 years, has likewise been shaped by environmental conditions, interacting with human culture and technology (McMichael, in press). The constant struggle with infectious agents, dietary stresses and environmental toxins has left extensive imprints on our genetic makeup. Cultural evolution, too, has had major consequences for human biology, social wellbeing and health.

Today we must find a sustainable way of living. The issues are complex, communities are naturally conservative, and democratic governments have limited time horizons. We may find technologically clever ways of lessening our environmental impact and thus slowing the depletion of our natural resource base. The application of biotechnology, the use of precision farming and water management, and the use of alternative energy sources may all be part of the solution. However, we will also need to reform our social priorities and economic systems. We will need to constrain human numbers and levels of waste-generating consumption in order to protect the life-supporting systems of the natural environment. To achieve the Sustainability Transition, we must understand the ecological frame within which we exist.

The essence of the Sustainability Transition, I suggest, is that, in future, sustainable human societies will:

- Consume primarily nature's "flows" (that is, live off the "interest" – such as renewable energy, regenerate harvests – while conserving environmental capital).
- Increase society's "capital" stocks (human resources and civil institutions)

The twenty-first century will pose a mighty challenge. Demographic stresses with ageing populations, social disorder in large cities, ethnic fragmentation as nation-states falter, and conflicts over scarcity may all increase. As the world economy globalises, as geographic regions connect, as trade liberalises and transnational corporations assume greater control over international consumerism, optimists predict that gains in material wealth will bring social progress and improved health. Others, however, foresee an amplification of the rich-poor divide, a heightening of political and economic tensions, an indifference to environmental management, and a deterioration in health and life expectancy.

There is a grand challenge here for those of us researching, teaching and practising public health. There is a radical need for a systems-oriented perspective, for an understanding of ecological sustainability, and for a recognition of the deeply layered social, economic and other influences on the population's health. There is need for socially enlightened integration of new biotechnologies into medicine and into public health.

The Queen Mother's impending one hundredth birthday is a testimony to the great gains made in population health in western societies during the past century. During the twentieth century we have doubled humankind's average life expectancy at birth, quadrupled the size of the human population, increased the global food yield six-fold, the production of carbon dioxide twelve-fold and the overall level of economic activity twenty-fold. The best, recent, estimate is that we have now exceeded the planet's carrying capacity by around 30 per cent (Loh *et al.*, 1998) – we are currently operating, globally, in ecological deficit. The rate of human-induced change in the world around us is dramatic, and quite unprecedented in history.

We cannot stand still at the crossroads contemplating the several

seemingly divergent concepts, promises and hazards of germs, genes and greenhouse gases. Rather, we must seek a path to the future that achieves a complementarity, perhaps a synthesis, of molecular biotechnologies with socially-oriented strategies to reduce inequalities in health and to contribute further gains to population health. Above all, we must do all of this in a way that is environmentally benign and ecologically sustainable.

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