PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Conclusions – scientific research and its implications

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Conclusions—scientific research and its implications

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SUMMARY

The organizers of this meeting felt that it would be appropriate to have two short papers at the end of this volume to summarize the key points that are of relevance to scientists and the insurance and actuarial professions. This was felt to be of particular importance given the very heterogeneous backgrounds of members of the audience at the meeting, namely, scientific, medical, legal, social and financial.

The objectives are to summarize the key issues in layman's terms—trying to avoid jargon, exaggeration and a partisan approach. In some ways my task is somewhat easier than Chris Daykin's job, since there are only four scientific and medical presentations compared with seven from the actuarial, social and legal side.

I will organize this brief report, which by definition will involve repetition of some of the points made in the scientific and medical papers in this volume, into three areas: (1) introductory comments on demography and evolution relevant to human genetics; (2) the scientific opportunities; and (3) a brief comment on their implications for the health and care of individuals.

1. DEMOGRAPHY AND EVOLUTION

I start with demography since it is important to keep in mind the changes that are occurring in our society in terms of life expectancy and the associated age structure of populations in the industrialized countries. The world's population continues to grow at a rapid rate, with most of the growth in the developing world, particularly Africa and Asia. Between 1990 and 1995, the world's population has witnessed its greatest increase in history. A medium global population projection for 2050 is 9.4 billion people compared with 5.7 billion in 1995. Over the period 1995 to 2050 the populations of the developing countries will have almost quintupled, with a further 6.8 billion people added. The highest rate of growth in the coming decades will occur in sub-Saharan Africa (table 1).

The age structure of the world's population differs markedly by region; in rich countries it is increasingly flat, while in poor countries the distribution decays rapidly with age. In the latter, the major killers remain infectious diseases (table 2). In the majority of the world's population infectious agents are key selective agents—determining the genetic structure of populations. Most of this mortality, but not all, is preventable by simple interventions such as adequate nutrition, clean water supplies, vaccines for the childhood infections and antibiotics. The barrier to prevention is not available technology—it is simple resources to buy the vaccines, drugs and food. It is worth reminding ourselves that in the not too distant past our own population was subject to similar influences from infectious agents. The mortality from a common childhood disease such as measles (a viral disease) was high in the UK until the early part of this century (Aaby 1992). Its rapid decline prior to any effective intervention (vaccines were only introduced in 1968) was due to a combination of nature and nurture—i.e. a better fed population and selection—acting on individuals before they entered the reproductive age classes—which act to favour those who would survive this infection and develop lifelong immunity (figure 1).

Bearing in mind these events in the not too distant past, where infectious diseases both dominated morbidity and mortality in the UK, and shaped our current gene pool, the situation today is very different. In the 1950s hospital wards were full of cases of polio and diptheria. Today, wards are dominated by older patients suffering from heart diseases and cancers. Our current survival curves, by comparison with those of developing countries, starkly reveal the benefits of bringing infection under control (for the time being) (table 3). An immediate consequence of this slow but steady rise in life expectancy is that in the very near future the age structure of our population will be dominated by elderly people with a very flat distribution and with large and growing numbers in the 75+ age group (Lutz *et al.* 1997). Life expectancy is greatest at present in Japan with 82.5 years for women and 76.3 years for men. These figures have improved considerably in the past few decades. By contrast, 30 years ago life expectancy in Eastern Europe was similar to that in Japan, but has not increased since, and may have declined in recent years. In most developed countries the trend for decreased mortality and fertility will result in very significant changes in the age distribution. In Europe, for example, the proportion of the total population in the age group above 60 will increase from its current level of 16 % to about 34–40 %

Table 1. *Population size (in thousands) of the ten most populous nations in the world in 1995 and in 2050 (UN population estimates and projections)*

nation	1995	nation	1996
China	1 220 000	India	1 533 000
India	929 000	China	1 516 000
USA	267 000	Pakistan	357 000
Indonesia	197 000	USA	348 000
Brazil	159 000	Nigeria	339 000
Russian Fed.	148 000	Indonesia	318 000
Pakistan	136 000	Brazil	243 000
Japan	125 000	Bangladesh	218 000
Bangladesh	118 000	Ethiopia	213 000
Nigeria	112 000	Iran	170 000

Table 2. *Causes of death in sub-Saharan Africa 1985 (Jamison et al. 1993)*

cause of death	total deaths (thousands)	percentage
perinatal	672	9.3
infectious diseases	3403	47.2
cancers	42	3.4
circulatory system	909	12.6
maternal	48	0.7
injury	294	4.1
other	1635	22.7

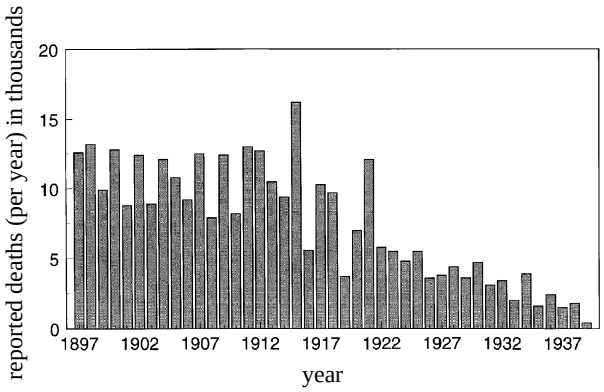

Figure 1. Deaths attributed to measles in England and Wales over the period 1897–1939.

Table 3. *Demographic parameters by region 1985–1990*

region	population (millions) 1985	life expectancy at birth (years) 1985–90
industrialized market economies	760	76
industrialized transition economies	416	70
Latin America and Caribbean	402	67
sub-Saharan Africa	556	52
Middle East and North Africa	376	60
Asia and Pacific	2434	64

Table 4. *Age-standardized death rates (per 100 000 people) for selected causes and industrialized countries 1985 (Jamison et al. 1993)*

	market economies	
cause of death	males	females
infectious diseases	48.3	28.5
tuberculosis	2.7	0.8
acute respiratory infections	37.3	22.2
neoplasms	264.6	154.4
circulatory and certain degenerative diseases	516.7	323.3
ischaemic heart disease	222.4	108.8
cerebrovascular disease	102.7	83.1
other cardiovascular diseases	138.1	98.7
diabetes	14.2	14.0
other degenerative diseases	39.2	18.6
complications of pregnancy	—	0.2
perinatal conditions	7.5	5.8
injury and poisoning	79.5	31.8
ill-defined causes	26.8	18.7
all other causes	127.5	72.7
total	1070.9	635.3

by 2050. This has many implications for the costs of healthcare, the social security system, the provision of homes for the elderly, particularly when combined with the fall in average family size and the growth of single parent families. The types of diseases that will dominate will change with, for example, neuro-degenerative diseases becoming more prevalent as is so clear in the United States at present. However, aside from diseases of the elderly, causes of mortality in the middle age groups are changing. AIDS is the leading cause for men in the 20–40 age group in the USA at present—and for females, AIDS is now in the top five for the same age group. Fortunately, that pattern will not pertain in the UK, or more broadly in Europe, perhaps with the exception of France and Switzerland. That our current gene pool in Europe has been strongly influenced by infectious agents is not in doubt, but today most view our population as not subject to natural selection arising from the survival of the fittest—since so little mortality occurs before the reproductive ages. In the absence of any catastrophic invasion by a new and lethal pathogen, this situation will pertain for the foreseeable future—where social, cultural and behavioural factors will determine mate selection and the resulting recombinant genomes. It is very difficult to predict the direction of evolution in such circumstances, or more precisely, to predict how genetic diversity will change over time. Given our increasingly global mixing habits, our own gene pool will increasingly be influenced by matings across ethnic or geographic boundaries.

The current pattern of disease that induces premature mortality in the UK, is well captured by the World Bank's concept of a DALY (disability adjusted life years lost) which is, in essence, years of life lost from life expectancy as a consequence of particular diseases (Jamison *et al.* 1993) (table 4). Diseases increasingly cause mortality in 'old age'—but our concept of 'old

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age' will of course continue to change. Many believe that there is still considerable room for further improvements in life expectancy.

2. SCIENTIFIC OPPORTUNITIES

Turning now to the key scientific talks at the meeting, the opening by Sir Walter Bodmer conveyed the excitement felt by scientists working in the field of human genetics. It is without doubt a very rapidly advancing field and, moreover, the research will have many implications not only for health and medicine, but for biology in general as we move from descriptions of the genomes of particular species such as *Homo sapiens*, to the more challenging and interesting questions of how does the genetic code, via the genes which form this code, determine biological function—or in the case of disease—malfunction. It is important that there is a wide understanding that the drive to sequence the human genome and to map its constituent genes is not just to simply facilitate genetic screening or to encourage genetic engineering, but to understand how living organisms function. For medicine, of course, if you understand how something functions in precise detail, it helps to develop interventions to maintain this function when a fault or a mutation occurs. Mapping and sequencing the 80 000 odd genes in the human genome will be completed much earlier than expected—perhaps in the very early part of the next century—and much attention quite rightly is centred on the achievement of this goal. But the real challenge will be discovery of function and process, and the real gains for health, will occur via the latter endeavour.

Walter Bodmer stressed the potential value of genetic screening, perhaps via DNA chips (a new technology), and the unique opportunity presented by genetic information for diagnosis and eventual prevention. However, two points of caution should be noted. First, many find it difficult to distinguish between genetic information obtained by a test or via screening, from that obtained by biochemical or physiological methods or techniques. Here I differ in view with that expressed by Professor Harper. The genetic information is the code of instruction, the other is the transcription or expression of that code. This point needs further discussion by the scientific and medical communities to help allay fears that genetic information is somehow more intrusive. It *may* be more precise, but biochemical, immunological or physiological measures can also be precise, and they will become increasingly so in the coming decade. A simple example is the measurement of blood pressure and its relevance to the occurrence of certain diseases.

Turning to the issue of population screening, which Walter Bodmer advocated as a possibility to detect rare but lethal diseases or to discover predisposition to complex multifactorial or polygenic diseases. Technically, this is possible and will become increasingly so for a much broader range of diseases. Putting aside the social and ethical problems raised by such screening I am doubtful that it will be used in practice in the foreseeable future because of cost and the difficult task of demonstrating cost-effectiveness, a point made by Sally MacIntyre. Take, for example, past controversies that surround routine mammograms to detect early breast cancer or the current debate on tests for prostate cancer. Immunological screening is also possible via non-invasive methods such as saliva to detect the presence or absence of immunity to serious childhood diseases—the capability has been present for some time. It is the costs of such screening and the benefits arising that will need very careful study—via long-term and somewhat difficult epidemiological research. Even if screening for a particular disease is cost-effective, there is no guarantee that it will be used. The example of hepatitis B is illuminating. Selective screening is highly effective, but not routinely done; but weighted against other priorities in NHS expenditure, the disease is too rare to emerge high on the priority list in the sense of introducing mass vaccination of all children or adolescents.

John Bell gives precision to why the biomedical research community is so excited by progress in medical genetics at present, in a very direct way since his group at Oxford are at the forefront of international effort in the search for associations between genetic background and complex polygenic or multifactual diseases. He stressed the difference between monogenic and polygenic/multifactorial disease and reminded us that a particular phenotype, in terms of the presence of serious disease, may arise via a variety of mechanisms. This is of particular importance for the polygenic diseases, where for example, particular mutations of specific genes, may only account for a very small fraction of the total disease burden. Breast cancer is a good example, where currently identified mutations in two particular genes only account for 5 % of total cases. As such, these mutations are not particularly good, on a population basis, for detecting predisposition to disease for health insurance purposes. John Bell also stresses the fact that human genetic studies were only part of the process to develop a better understanding of predisposition to disease or the prediction of risk. Epidemiological study must be combined with genetic information to sort out the relative, or quantitative contribution of genetics versus environment or lifestyle.

Epidemiological study is essentially the study of patterns of disease within populations. It is a very interdisciplinary area of medicine, involving genetic, molecular, immunological, statistical, mathematical, behavioural and field study within communities or populations. Detailed long-term cohort epidemiological studies are essential to sort out quantitatively what predisposition means, both in the obvious sense of if disease will occur and the probability of occurrence stratified by various factors, such as sex, age, socio-economic status, and more importantly for insurance purposes (whether health or life insurance), when it is likely to occur. The former is somewhat easier to determine—little attention has as yet been given to the latter, namely when and the associated uncertainty surrounding the question of when. Take the examples of breast and colon cancers. Many of us will succumb to cancer in our old age, but we all hope it will be a long time away from the present. So the question is not

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whether we are predisposed to die of a particular cancer (for genetic reasons) but whether we will do so at an earlier age than average life expectancy. The question of when is much, much more difficult to answer with precision in the absence of detailed long-term longitudinal cohort-based epidemiological data. Very complex epidemiological study designs are required to sort out associations between genetic background for polygenic disease and probability of death or illness by age. Such studies inevitably have to involve very large sample sizes and occur over long periods of time. Digital records of the 'life history' of an individual's disease events contained within General Practitioner databases may provide a rich source of information in the coming few decades.

Given that a close relationship between genetics and epidemiology will be required to give quantitative precision to the role of genetics in predisposing to disease it is not clear that resources will be available to carry out large-scale epidemiological studies. In their absence much guess work will surround the likely quantitative relationships that are needed to assess risk associated with genetic background. Cohort long-term studies are required, but they are unglamorous in today's environment of molecular experimental studies and do not, in terms of scientists' careers, yield results quickly. Molecular genetics is fashionable, exciting, and can lead to quick results to further an ambitious and able young scientist's career. Hence two problems arise: we need to attract and retain good minds to work in this field and we need to fund such studies properly. It will need a concerted joint effort by the NHS research directorate and the research councils to encourage and preserve such long-term epidemiological studies and to encourage closer integration with genetic research.

John Bell also reminded us that even for some of the complex polygenic diseases cross-sectional studies are, in a few cases, revealing high relative risks for common diseases, associated with particular genetic backgrounds. In the context of health insurance, the implications of recent results have not been fully digested at present. So although multifactual diseases are complex and difficult to study, significant associations are already being found—and this trend will surely accelerate.

3. IMPLICATIONS FOR INDIVIDUAL HEALTH AND CARE

Many have pointed out the benefits that might arise from the discovery of genetic association or predisposition to disease in terms of interventions. As yet, these benefits are largely unrealized for the common disorders of middle or old age, but progress is likely given the intense interest from the pharmaceutical industry. Chris Higgins provides a clear exposition of the technique of gene therapy and its promise. I can add nothing further to what he said except a minor caution. It is a very exciting and promising avenue of research, but as yet the technique has not proved of benefit in clinical terms. For commmon diseases such benefit is uncertain at present and a long way down the line. In the questions asked to Professor Higgins, perhaps 70% were concerned with safety—hence the public acceptability and safety issues must be addressed carefully. Interventions to improve health via knowledge of genetic background are more likely to arise from more conventional drugs-based therapeutic approaches in the shorter-term.

Professor Harper addressed the issue of the interaction between the medical and insurance industries. I share some of his concerns, but by no means all. It is difficult to separate knowledge based on biochemical or physiological tests to that based on genetic screening. However, many strongly agree with his view that wide-scale population-based screening will not be implemented rapidly. For cost reasons this seems unlikely in the foreseeable future.

Perhaps the biggest surprise to a scientist reading the papers in this volume and presented at the meeting may be the simplicity of the method by which the actuarial profession assesses an individual's risk. You might be excused for thinking that the insurance industry is hiding something from the scientists and the public to lull them into a false sense of security. But via discussions that took place at the meeting, the process appears to be somewhat simpler than many imagined. In this sense, we should feel more confident that genetic testing, with all its inherent problems of cost and lack of precision for the common diseases of middle and old age, will be slow to enter into actuarial thinking. That will give us all valuable time for very full and open discussion of the issues and problems over the coming years. It is vital that this discussion takes place in the public arena.

The scientific and medical professions' excitement about human genetic research lies in its potential to improve our understanding of how biological systems function, and hence, in the search for better therapies to improve health and prevent premature mortality. Life expectancy will continue to rise, but it appears unlikely that the new technologies will induce rapid change in the rate at which it rises. Ultimately, evolutionary biologists argue, there is a limit to how much life expectancy can increase by. Many suspect we are a long way from that limit.

I hope the meeting and this volume will leave many with a sense of optimism about the dialogue that has been promoted between the actuarial industry and the scientific and medical research communities, and I do hope it is a continuing one, to develop better understanding of the aims and problems of both professions.

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