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SUMMARY

The range of genetic diversity within human populations is enormous. Genetic susceptibility to common chronic disease is a significant part of this genetic diversity, which also includes a variety of rare clear-cut inherited diseases. Modern DNA-based genomic analysis can now routinely lead to the identification of genes involved in disease susceptibility, provides the basis for genetic counselling in affected families, and more widely for a genetically targeted approach to disease prevention. This naturally raises problems concerning the use of information on an individual's decisions, but for employment, and health and life insurance.

1. INTRODUCTION

We are all different and many of the differences between us are genetic. This can readily be seen from pictures of identical twins at any age, which emphasize that most of the outward differences by which we recognize each other must have a genetic basis. These outward differences are paralleled by fundamental differences in our chemical make-up which, in particular, influence disease susceptibility.

Each time a sperm meets an egg, the potential for a genetically new individual is generated. The chromosomes, which can be seen in the centre of a cell when it divides, have at their core the enormously complex chemical, DNA. DNA carries the language of life. Our knowledge of its structure, which was deciphered by Watson and Crick just over 40 years ago in Cambridge, at the Laboratory for Molecular Biology, began a revolution in our chemical understanding of the process of inheritance which continues to this day and beyond. The DNA language is written with four letters which are shorthand for its basic chemical constituents, namely A, G, T and C. Each of the 23 pairs of human chromosomes carries about 120 million letters-worth of the DNA language. One member of each chromosome pair comes from our mother and the other from our father. The sex-determining chromosomes are X and Y, where XX is a female and XY a male.

The genetic technology revolution means that we can now decipher and read the language of the DNA in our chromosomes at will. The aim of the Human Genome Project is to obtain the complete sequence of these letters along all the chromosomes, while on the way locating the genes on the chromosomes. Genes are the functionally relevant segments of the genetic language. This ability to read the genetic sequence has dramatically changed our understanding of human disease, our ability to deal with it, and indeed to study any individual differences. It is that ability and knowledge which underlie the burgeoning biotechnology industry. Those of us who have been involved in the idea of the Human Genome Project since 1980 or even before, were perhaps surprised that only five or six years ago it was hard to persuade the pharmaceutical industry (and even the Royal Society) to take an interest in this area. Now, however, the situation has changed dramatically and the pharmaceutical industry sees the outcome of the Human Genome Project as the basis for its future drug discoveries (for general background see Bodmer & Cavalli-Sforza 1976; Bodmer & McKie 1994).

2. POPULATION GENETICS

Mendel's laws, which effectively describe the basic patterns of inheritance in families, were rediscovered at the turn of the century. The ABO blood group system, by which we match individuals for blood transfusion, was discovered at that same time. The ABO blood types were probably the first clearly defined human genetic differences that were shown to follow Mendel's laws in families, but which could also be studied in human populations. The frequencies of the ABO blood types were shown to vary from one population to another. Thus, the frequency of type B, which is relatively low in the periphery of Europe, including Great Britain, is much higher in certain Asian countries, notably India. It was soon realized that populations could be classified, at least to some extent, by the frequencies of such genetic differences within them. Indeed, this is perhaps the only scientifically appropriate way to define a human population.

With the discovery of more blood groups and, in particular more recently, of the huge amount of individual variation that can now be detected at the DNA level, much information can be gained that can tell us about the history of our own species. Thus, it is such studies that have strongly supported the view that modern *Homo sapiens* came out of Africa, probably no more than 150000–200000 years ago. It is, therefore, within that time-span that selection for light complexion occurred to compensate for the otherwise low levels of vitamin D that those humans who migrated

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too far North would have been able to synthesize in low sunlight. This skin colour difference is now the major determinant of skin cancer, which occurs several hundred-fold more frequently in white-skinned people who live in the tropics than in dark-skinned people.

In Northern Europe, on average, about 16% of the population is Rhesus negative. This condition, which is essentially a defect in the synthesis of a particular chemical product found on the surface of red blood cells, has no obvious clinical effect on its own. However, when Rhesus negative women have more than one Rhesus positive baby, this often gives rise to a severe disease called haemolytic disease of the newborn. Because of the pattern of the Rhesus negative frequency distribution, this disease is essentially unique to Northern Europeans and, fortunately, can now be prevented by appropriate prophylactic measures. Some years ago, Luca Cavalli-Sforza noted that the frequency of Rhesus negativity might reflect a gradient of change across Europe, and found other genetic differences with a similar pattern. Putting together the data available already some 25 years ago led Cavalli-Sforza to suggest that the gradient of genetic differences across Europe reflected the expansion of agriculturists from the Fertile Crescent in the Middle East outwards, starting some 10000 years ago. More recent studies, using a greater variety of genetic markers, have strongly supported this intriguing idea which brings together the work of human geneticists, physical anthropologists and archaeologists. Now there is the opportunity to delve even more deeply, with the currently available technology, into the origins of modern populations throughout the world (see Bodmer 1992; Cavalli-Sforza *et al*. 1994; Stringer & McKie 1996).

3. GENETIC DISEASE AND SCREENING

Another genetic difference that is relatively common only in Northern Europe is that which determines the inherited deficiency called cystic fibrosis. This is a very serious disease which results in malabsorption of fluid. While modern medical care can keep people with cystic fibrosis alive longer and longer, there is still no satisfactory cure and their average lifespan is much less than normal. The disease occurs, for example, in most parts of Britain with a frequency of about 1 in 2500, and is due to a defect in a gene that controls the transport of certain chemicals from outside to inside the cell. The discovery of this defect was one of the major initial successes of the Human Genome Project. The pathway was traced from the family to a knowledge of where the genetic defect lay on the chromosomes, and thence to the gene itself, without any prior understanding of what might be the biochemical nature of the defect in people with cystic fibrosis.

Once found, the gene's DNA sequence immediately revealed its potential transport function. Now experiments are underway to try and correct the disease defect at the level of the gene itself. Knowledge of the gene's function also leads to innovative approaches to selecting for drugs that might compensate for the defective gene function which causes cystic fibrosis.

The most specific outcome, however, of the discovery of the cystic fibrosis gene is its application to early diagnosis. Carriers of a defective version of the gene are themselves perfectly normal. However, if they mate with another carrier they will produce, on average, one quarter of offspring with the disease. Carriers can now mostly be readily identified. In Britain, about 80% of carriers all have the same particular defect in their cystic fibrosis gene, while the remaining 20% have a whole variety of other changes with the same or similar effects. Thus, while not all carriers could be detected by a population-based screen for the common cystic fibrosis mutation, more than 95% of the parental combinations giving rise to the disease involve at least one parent who carries this common mutation. One population-based strategy for identifying couples at risk of producing cystic fibrosis offspring, would therefore be to screen the population for the common mutation, and then test only the partners of those which have this mutation, for this same mutation, or any other defect in the cystic fibrosis gene. At the moment, apart from counselling such individuals as to their risks, the only positive action that can be taken is to offer an elective abortion if genetic tests show that the foetus would have cystic fibrosis, or to use *in vitro* fertilization, coupled with genetic testing, to screen out affected embryos. This, of course, depends on a couple being willing to accept the idea of an abortion, or *in vitro* fertilization, in order to have a subsequent unaffected child. Unless a mother was prepared to take this step, there would be no case for doing the screen for the cystic fibrosis mutation.

The proper implementation of such a programme requires not only the provision of the resources for doing the genetic tests, but also the provision of counselling through genetic clinics, and of course the clinical resources needed for carrying out the elective abortion or *in vitro* fertilization. In future, when it may become possible to treat individuals with cystic fibrosis satisfactorily, it may be even more important to provide the genetic screening resources and so identify offspring at risk, since starting a treatment early is likely to be quite critical.

So far it has not been considered cost-effective to screen in this way for just one inherited disease, even one as relatively common as cystic fibrosis. However, it should be remembered that every child is now screened for another defect, phenylketonuria, which can be corrected simply by providing an appropriate diet. Otherwise, this defect leads to severe and untreatable mental retardation. More and more diseases like cystic fibrosis are being characterized at the DNA level, and if one could, say, do a population screen for a hundred such diseases, the tests could well become cost-effective and relatively straightforward to do. It is very important to point out that while the basis for first discovering the defects at the DNA level in these genes involves the high technology of DNA manipulation, the actual application of the DNA diagnostic tests is becoming cheaper and cheaper. Eventually, there may be some form of chip-based technology which could make it easy to test an individual for a very large number of such genetic differences relatively cheaply,

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using only a small sample of blood, or even just a smear of cells obtained from a mouth wash.

The technology for finding disease genes, which has already been briefly mentioned, arises from the ability to identify the positions on the chromosomes of genes which carry the defect that leads to any particular disease. This can be done by identifying the known functional genes around the position to which the genetic basis for a disease maps on the chromosomes, and then testing each of these functional genes as candidates to see which one is mutated or altered in a way that explains the pattern of the disease as it is inherited in the family. That is the way the cystic fibrosis gene was found. Soon, however, when the Human Genome Project reaches its ultimate goal, which could easily be by the turn of the millennium, it should become possible simply to look up a database of genes and their locations once a gene has been positioned by standard family analysis, and through that identify possible candidate genes. Some knowledge of the nearby gene sequences or functions might indicate which are the best ones to test for initially. Whatever the approach, the identification of disease genes becomes ultimately a matter of testing candidate genes for mutations in affected, as compared to normal individuals.

The principle of this approach to identifying disease genes can be illustrated by an example from my own field of cancer research. Cancer is a disease where one can nearly always do something to redress the effects of susceptibility to a cancer by detecting it early.

A clear-cut inherited susceptibility to bowel cancer was first described in the mid-1920's at St Mark's Hospital in London. Bowel cancer is one of the commonest of cancers, and perhaps the commonest not caused by cigarette smoking, giving rise in this country to about 19000 deaths per year. The specific 'dominantly' inherited disease called 'polyposis', accounts for about a half of one percent of all the cases of bowel cancer. The gene was first located and then found and identified just in the way the cystic fibrosis gene was found. There are now, therefore, clinics throughout the country that serve the needs of those who know that they have got polyposis in the family. Surgical intervention to remove the major part of the colon allows affected individuals to have a reasonably good quality of life with an expectation of life that is not materially different from what it would be if they did not have the disease–and that is surely a considerable benefit. Because the genetic basis of the disease is known, the individuals at risk within a family can be identified through genetic tests at the DNA level at a much earlier time than is possible by clinical investigation.

The dominantly inherited nature of the disease means that an individual with polyposis will, on average, pass it on to half his or her offspring. However, because of new mutations in the polyposis gene, about 40% of cases of polyposis in the population at large are 'sporadic', meaning that they have arisen afresh and will not be associated in families with affected relatives. Thus, if polyposis individuals are only identified through Cancer Family Clinics, then these sporadic cases will be missed. However, in principle, if the whole population could be screened for mutations in the polyposis gene, all new cases could be identified. This would help not only those sporadically affected individuals to identify and help themselves, but also their children. Technically, however, screening for polyposis mutations is more difficult than in the case of cystic fibrosis, since there is no one very common mutation, and so the screen must be able to identify changes over a considerable stretch of DNA. Once again, however, the technology is advancing rapidly so that it will probably soon become quite easy to do this. The question will then be raised: is it worth doing a population-based screen for polyposis mutations? In this case, there can be no doubt that when individuals with a mutation are identified, they will gain considerable clinical benefit. The costs at the moment are still high. But, if such tests could be done for a whole range of diseases, in particular dominantly inherited cancers of a similar nature to polyposis for which early detection is of clear benefit, then population-wide screening could well be justified on a cost–benefit basis (for background see Bodmer (1994) and Cunningham & Dunlop (1996)).

Breast cancer susceptibility genes have been identified which are just like the polyposis and other bowel cancer genes (Szabo & King 1995). One of the major differences, however, between bowel and breast cancer is that, by using flexible fibre optics, it is possible to see pre-cancerous growths in the bowel, whereas there is no comparably effective technique for detecting pre-cancerous breast growths. The presence of these pre-cancerous bowel growths is an unequivocal indication of the subsequent risk of a cancer, but that risk can be removed simply by removing the easily visible growth. For the genetic information on cancer susceptibility to be really useful, reliable early detection of a cancer is crucial. This works for bowel cancer because, by the time the early growth is detected, it is very unlikely to have spread to other parts of the body and so local removal is effectively a cure. The main approach to early detection of breast cancer is through mammography which is, unfortunately, not very reliable, especially in younger women. Thus, if mammography does not reveal any abnormality one cannot be secure in saying that there is no cancer. Mammography cannot, therefore, be used reliably as a basis for detecting early cancers at a stage when surgery can provide a cure. While those women with a breast cancer gene mutation whose mammography reveals a lesion can benefit from its removal, those where mammography is negative cannot be assured that they will not develop a cancer which may prove difficult to cure by surgery and available drug therapy. This raises the very difficult question as to whether it is appropriate to recommend prophylactic bilateral mastectomy, namely early removal of both breasts, in cases when one is at high risk of getting a breast cancer. There is no doubt that such an approach will remove the vast majority of the 80% risk of getting a breast cancer for women who carry the relevant mutation, just as in polyposis removing most of the bowel removes most of the risk of getting a bowel cancer. Such

prophylactic surgery, however, raises the obvious issue as to its acceptability and, of course, also raises the undoubted need for better tests for early detection of the presence of the cancer itself and not just for the susceptibility to it.

4. MULTIFACTORIAL DISEASE

The diseases I have discussed so far have clear-cut patterns of inheritance, where sometimes treatment can be effective and where, as in the case of cancer in contrast to many other inherited diseases, the onset of the disease is relatively late in life. There is, however, an inherited component to most diseases, namely a susceptibility or tendency to get the disease that may be greater if one carries certain genetic markers. Such genetic tendencies are, however, far from all or none and are reflected, for example, in the relatively high frequency with which relatives of individuals who have colon cancer tend also to get it. Thus, the proportion of first degree relatives (namely offspring or parents of individuals who themselves have colon cancer) that also have colon cancer, is some three-fold higher than the rate observed in the population as a whole. Such increases in the 'relative risk' of disease in relatives, of the order of two- to three-fold, are quite common. How can one identify the genetic contribution to such an increased relative risk? Can individual genetic factors be identified that are responsible for all, or at least a significant part of, that increased risk?

The ideas for doing this can be illustrated by the example of the class of diseases which are called 'autoimmune'. These arise when the body's immune system, which normally protects us from foreign infections by viruses, bacteria, parasites and moulds, malfunctions and starts attacking the body's own tissues. Amongst diseases caused by such autoimmune attack are rheumatoid arthritis and juvenile onset insulin-dependent diabetes, for which there is very clear evidence of a genetic tendency, but it is not all or none.

The detection of the major genetic contribution to such diseases came from the study of individual differences that are like the blood group differences, but which were studied in order to match people for transplantation. The reason that a small piece of skin grafted from any one person onto another does not survive is because we all differ with respect to a set of marker tissue types, or markers of the 'HLA' system, which the body recognizes as foreign. If I have a piece of someone else's skin grafted onto mine, it will be rejected as if it were an infection because of the HLA differences that are almost certain to exist between myself and the skin donor. One of the problems facing successful organ transplantation is to combine matching in order to reduce the foreignness of a graft, with the use of drugs to inhibit the body's immune system and prevent immune rejection because of the foreignness of the donor's graft.

There are hundreds of different HLA types which can occur in billions of different combinations. However, the HLA types are controlled by a cluster of genes that lie close together on one of the human chromosomes, so that it is this cluster which is passed on from parent to offspring. This means that, within a family, approximately one quarter of pairs of sibs chosen at random will be truly matched, and that is the basis for using HLA-matched sibpairs for bone marrow grafting. Only when there is that extent of matching do the grafts really work well. We now know that the protein molecules which carry the HLA types play a key role in the way the body's immune response functions.

The HLA types, as might be expected, differ enormously in frequency from one population to another. It is often useful to consider the frequencies of combinations of types, such as the combination A1, B8 and DR3 which is particularly common in Britain and certain other parts of Northern Europe. This combination may represent a type that was present in the original populations that defined the Celtic fringe of the British Isles and Ireland (Bodmer 1992). European populations that have migrated to other parts of the world can readily be traced by their HLA types by looking at such combinations. Once it was realized that the HLA proteins were involved in aspects of the control of the body's immune response, it became natural to ask whether any of the HLA types might be associated with disease-causing immune responses, such as in autoimmune disease. Is there some effect of a particular HLA type on disease susceptibility? That indeed is what was found to be the case, and quite strikingly so in some cases.

Ankylosing spondylitis is an autoimmune disease, sometimes called 'poker-spine', in which the vertebrae tend to fuse together as a result of an autoimmune attack. It is an unpleasant, although not generally a life-threatening disease. When HLA types were looked at in people with ankylosing spondylitis and controls without, it was found that the HLA marker B27 occurred in virtually all individuals with ankylosing spondylitis, but in only 5–10% at most of the normal population, namely that without ankylosing spondylitis. There is, thus, absolutely no doubt of the enormous impact of having B27 on the chance of getting ankylosing spondylitis, since without it the chance of getting the disease is exceedingly small. On the other hand, only a relatively small percentage of individuals with B27 get ankylosing spondylitis. That is a characteristic of what is meant by multifactorial disease, or disease tendencies or susceptibilities. Ankylosing spondylitis is, fortunately, a comparatively rare disease occurring in only a fraction of a per cent of the population, and mainly in males. It is mostly diagnosed satisfactorily without doing a B27 test. On the other hand, Dr J. Bodmer, working with Dr F. H. Hill and Dr A. G. S. Hill in studying ankylosing spondylitis in women, where it is a much less severe disease, found some 20 years ago that it was nevertheless just as strongly associated with B27 (Hill *et al.* 1976). Ankylosing spondylitis in women was often missed at an early age, and so patients were told to go home because 'they just had a bit of lower back pain and should not worry about it'. However, that was wrong, and when the B27 test was done it was found that this could help decrease the average time between initial symptoms being reported to a doctor and the

actual diagnosis from often 8–9 years to a maximum of a few years. They then argued that appropriate physiotherapy could help those women with ankylosing spondylitis, especially if it was started soon enough.

Similar HLA associations are found with rheumatoid arthritis and coeliac disease, which is a sensitivity to gluten found in wheat and other cereals. Haemochromatosis is an example of a disease associated with HLA type A3, but which has not appeared at all to be a disease connected with immune problems. The primary defect appears to be connected with an inability to deal with an accumulation of iron. Very recently, through finding out about other genes in the neighbourhood of the HLA cluster of genes, a candidate gene has been found that is quite different from A3, though distantly related to it, which appears to be responsible for haemochromatosis. In this case, the HLA type A3 has just acted as a marker pointing to where that other gene might be, just as in the 'positional' cloning of genes for cystic fibrosis and polyposis using family material. This approach suggests a way of finding genetic components to disease susceptibility without any knowledge of their functional basis, even when the disease is complicated and multifactorial (see Tomlinson & Bodmer 1995).

Twin studies can play an important role in telling us to what extent there might be an inherited component to a particular disease. It was Francis Galton, Charles Darwin's cousin, who in the late 19th century first pointed out, before anything was really understood about genetics, that twin differences could be used to study inherited susceptibilities. Thus, we can ask what is the chance, if an individual has a particular disease and has an identical twin, that this twin also has the disease? This chance is called the 'concordance', and the same question can be asked for non-identical twin pairs. Galton argued that, if the identical twin pair concordance was clearly greater than that for non-identical twin pairs, then that provided strong *prima facie* evidence for an inherited component. For example, one of the most famous, accurate and complete twin registers, from Denmark, shows that there is a significant excess of identical over non-identical twin concordance for mental deficiency, manic depressive states, hypertension and even tuberculosis. These are then the sorts of diseases where the aim is to identify susceptibility genes, like B27 for ankylosing spondylitis. The aim of identifying such genetic susceptibility factors is not only to help understand the nature of the disease, but also, if an individual is identified who has, say, a greater risk genetically of hypertension, then something may be done about it. This could, for example, be a more rigid diet or the use of medication to control blood pressure to help bring their risk back to the norm. The aim of such an approach, which is effectively genetically targeted disease prevention, is to bring the risk of those individuals identified as having an increased risk back to the norm. Thus, such studies are directed both at understanding the nature of the diseases through the genetics and then applying that knowledge to improving disease prevention by targeting it to genetically identified individuals at higher risk.

5. INSURANCE IMPLICATIONS OF GENETIC SUSCEPTIBILITY TESTING

There is no doubt that each particular example of this approach to disease prevention will need extremely careful investigation. There is, furthermore, no point whatever in doing a genetic test, except under experimental conditions, unless something can be done about it. A population-based screen for, say, a genetic risk factor for hypertension, would only be introduced if it was clear that the result of the test could help bring the risk of those individuals identified as having a higher genetic risk more or less back to normal. There may be some cases, for example Huntingdon's disease, which is a late-onset severe nervous and mental degeneration, where people may simply want to know whether they are at risk in order to plan their own lives. In that case, the choice of whether someone should be tested must be left to the individual themselves. In general, it should be a golden rule that the application of genetic knowledge will only occur if there is something that can be done about it.

What might then be the implications of our new and rapidly expanding genetic knowledge about human disease for the insurance industry? First, this knowledge is enabling us to deal with clear-cut Mendelian genetic diseases. There will, in future, be almost no such disease for which the gene cannot be found, and so the individuals at risk will be identified. In principle, for any such disease it should be possible eventually to do a population-based screen in order to provide medically useful advice, such as in the case of cancer prevention or cure, by catching the disease early. In other cases, there may be specific cures or approaches to prevention, while in yet others where nothing can be done, it may only be possible to offer elective abortion of those foetuses shown clearly to be at risk genetically, or selective *in vitro* fertilization. The key question is when will it be appropriate to do a population-based screen? This must be very clearly distinguished from having family clinics to which individuals go when they know, or suspect, that they have a disease in the family. In the latter case, one is dealing with individuals who are already aware that they have a family problem. Multifactorial disease where, as I have indicated, there are approaches to identifying the specific genetic factors involved, will as I have emphasized, only become relevant when it is clear that a genetically targeted disease prevention strategy will work, and that of course will require a fair amount of investigation.

A particularly important question that arises from these advances in genetics is who needs to know about an individual's genetic susceptibility make-up? Is someone who knows that they are at risk of Huntingdon's disease obliged to tell their spouse, or intended spouse? Or to tell their children? Or their relatives? Could employers ever need to know about genetic susceptibilities of employees?

When it comes to insurance there is a very clear need to separate the implications for health from life insurance. We are fortunate in this country in having a National Health Service that covers individuals

according to their ability to pay, with no respect to the severity of disease—insurance is based on solidarity not mutuality. This means that those with diseases such as polyposis or cystic fibrosis should be able to get satisfactory coverage through the existence of a universal National Health Service. I believe it is extremely important to maintain such universal coverage. The more it becomes possible to apply genetics to improve disease treatment, the more important it is to have universal health coverage so that insurance premiums do not need to be calculated as a function of an individual's genetic make-up. It is the existence of the National Health Service which means that, in my view, health insurance issues should not be of major concern in this country, in contrast to what might be the situation in other countries, such as the USA.

What then about the implications of the new genetics for life insurance? I believe that the situation is much simpler than it is sometimes made out to be. For a severe monogenic, i.e. a clearly inherited, disease with an early age of onset and little chance of long-term survival, life insurance is hardly relevant. On the other hand, for the clearly inherited severe diseases, such as cystic fibrosis, Huntingdon's disease and the cancer susceptibilities, there is obviously a potentially significant effect on survival, and it would be unfair not to take that into account in life insurance. However, the multifactorial diseases are, I believe, of little if any relevance for life insurance. As I have emphasized, a screening programme will only be introduced if the increased risk of those individuals identified as being genetically susceptible can be brought more or less down to the normal level. Since the insurance industry is often quoted as saying that even a two-fold increased risk is not enough for them to adjust their life insurance premiums, any genetically identified component of multifactorial disease susceptibility should, especially if targeted with prevention, be of no interest for life insurance.

Thus, I believe that the real question which remains is what does one do about life insurance for the severe later-onset monogenic diseases such as cystic fibrosis and Huntingdon's disease? Perhaps these diseases need to be dealt with in a way that is effectively outside the purview of the insurance industry itself. *Should there be legislation which proscribes the use of genetic information for the calculation of life insurance premiums, except in the case of an approved list of severe, simply inherited diseases*? This idea was suggested by Baroness Mary Warnock at a major genome meeting organized in London in 1991. The approved list of diseases would gradually increase by case law, and these are the diseases where an individual may have an obligation to inform an insurance company, and where the nation must decide on how to help such individuals. There could be an analogue of 'no fault' compensation which could still involve the insurance companies but with some support from government through, say, the Department of Social Security. It may well be that it is more important to provide social and medical care of such individuals than it is to provide them with the opportunity to have life insurance. Fortunately, these rare inherited diseases affect, collectively even, only perhaps 1% of the overall population, but in my view they do need to be specifically legislated for. The recent stand taken by the Association of British Insurers, arguing that they must have genetic information, even at this stage, suggests to me that voluntary regulation will not be adequate to control the situation.

The notion of an approved list may apply equally to employment. Colour blindness, for example, which is a perfectly normal difference occurring in about 7% of males in this country, can influence employment opportunities. Thus, while it is possible to get a pilot's licence if you are colour blind, I believe it is not possible to be a commercial airline pilot if you are colour blind. So there is no doubt that there may be certain genetic differences that are relevant to employment. In these cases, as in those severe clearly inherited diseases relevant for life insurance, there should perhaps be legislation that restricts the information that employers can have about the genetic make-up of an employee to a series of agreed situations, such as colour blindness and commercial piloting.

The House of Commons Select Committee on Science and Technology's report on human genetics is an excellent one (House of Commons report 1994–95). It is reassuring that the government finally accepted the recommendation for a Human Genetics Advisory Committee, which recently met for the first time. Deciding on these issues as to how genetic differences should be taken into account for insurance and employment, and the extent to which legislation and regulation should be introduced, are key issues for this Committee to address.

REFERENCES

Bodmer, W. F. 1992 The genetics of Celtic populations. *Proc. Br. Acad.* **82**, 37–57.

Bodmer, W. F. 1994 Cancer genetics. *Br. Med. Bull.* **50**, 517–526.

Bodmer, W. F. & Cavalli-Sforza, L. L. 1976 *Genetics, evolution and man*. San Francisco: W. H. Freeman & Co.

Bodmer, W. F. & McKie, R. 1994 *The book of man. The quest to discover our genetic heritage*. London: Little, Brown & Co.

Cavalli-Sforza, L. L., Menozzi, P. *et al.* 1994 *The history and geography of human genes*. Princeton University Press.

Cunningham, C. & Dunlop, M. G. 1996 Molecular genetic basis of colorectal cancer susceptibility. *Br. J. Surg.* **83**, 321–329.

Hill, F. H., Hill, A. G. S. & Bodmer, J. G. 1976 W27 and the clinical diagnosis of ankylosing spondylitis in women. *Annls Rheumatic Dis.* **35**, 267–.

House of Commons Science and Technology Committee. (Session 1994–95.) *Human genetics: the science and its consequences*. Volume 1.

Stringer, C. & McKie, R. 1996 *African exodus*. London: Jonathan Cape.

Szabo, C. I. & King, M. C. 1995. Inherited breast and ovarian cancer. *Hum. Molec Genet.* **4**, 1811–1817.

Tomlinson, I. P. M. & Bodmer, W. F. 1995. The HLA system and the analysis of multifactorial genetic disease. *Trends Genet.* **11**, 493–498.